Exhibit 3

UNITED STATES DISTRICT COURT FOR THE
NORTHERN DISTRICT OF OKLAHOMA

PETER POE, *et al.*, *Plaintiffs,* v. GENTNER DRUMMOND, *et al.*, *Defendants.*	No. 23-CV-00177-JFH-SH

DECLARATION OF ANGELA C.E. THOMPSON, M.D., MPH, FACOG

I, Angela C.E. Thompson, declare the following:

1. I authored the attached expert report, which Alabama submitted to a federal district court on May 19, 2023—*i.e.*, less than a month ago—in support of the Alabama Vulnerable Child Compassion and Protection Act.
2. I have reviewed Senate Bill 613 (SB 613) in Oklahoma, and I believe that the analysis in this expert report is largely applicable to SB 613.
3. Thus, I have agreed to permit the State of Oklahoma to utilize this report in opposing the motion for a preliminary injunction of SB 613. Here, as in Alabama, I believe that the law is based on medical facts and serves to protect minors from unethical experimentation.
4. It is possible that I could be available for live testimony, although that depends on my clinical schedule.
5. Aside from potential reimbursement for travel or research materials, I am not being compensated for the submission of this report.

I state under penalty of perjury that the foregoing is true and correct.

Executed on June ____, 2023.

s/#
Angela C.E. Thompson

UNITED STATES DISTRICT COURT FOR THE
NORTHERN DISTRICT OF OKLAHOMA

PETER POE, *et al.*,

Plaintiffs,

v.

GENTNER DRUMMOND, *et al.*,

Defendants.

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I state under penalty of perjury that the foregoing is true and correct.

Executed on June 12, 2023.

s/ Angela C.E. Thompson

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

BRIANNA BOE, *et al.*,	)	
	)	
Plaintiffs,	)	
	)	
UNITED STATES OF AMERICA,	)	
	)	
Intervenor Plaintiff,	)	
	)	
v.	)	Civil Action No. 2:22-cv-184-LCB
	)	
HON. STEVE MARSHALL, in his Official capacity as Attorney General, of the State of Alabama, *et al.*,	)	
	)	
Defendants.	)	

EXPERT REPORT OF
ANGELA C.E. THOMPSON, M.D., MPH, FACOG

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1. My name is Angela C.E. Thompson. I am over the age of 19, I am qualified to give this declaration, and I have actual knowledge of the matters stated herein. I am a physician certified by the American Board of Obstetrics and Gynecology to practice within the specialty of Obstetrics and Gynecology. I am also a Fellow of the American College of Obstetrics and Gynecology. My professional background, experience, and publications are detailed in my curriculum vitae, which is attached to this report.

2. I have been retained by counsel for Defendants to provide an expert opinion on the fertility considerations of administering to minors gonadotropin releasing hormone agonists (GnRHa), colloquially known as "puberty blockers," followed by supraphysiological doses of cross-sex hormones. This report discusses (a) the medical evidence regarding the risks such treatment poses to healthy biological function; (b) whether children in early puberty can assent to such treatment; and (c) the prospects of experimental fertility preservation techniques in early pubertal children who undergo such treatment. I may wish to supplement my opinions or the bases for them as new research is published or in response to statements made in my area of expertise.

3. I have not provided expert testimony in the last four years.

4. If called to testify in this matter, I would testify truthfully and based on my expert opinion. I am being compensated at a rate of $350 per hour. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony that I provide.

I. Summary of Opinions

5. The prevailing literature describes "gender affirming care" in the following ways: 1) Gender affirming endocrine treatments (Hembree 2017 pg 3869); and 2) A process of intervention known as "gender affirmation" (Rafferty 2018 pg 5). It is my professional medical opinion that the current "gender affirming care" ("GAC") regimen, specifically the regimen that

administers Gonadotropin releasing hormone agonist (GnRHa) medication (colloquially termed "puberty blockers") at Tanner Stage 2 of puberty, followed directly by supraphysiologic cross sex hormones, creates an iatrogenic disease state in otherwise developmentally healthy children and young adolescents that continues into adulthood. ("Iatrogenesis" is defined as the creation of additional problems or complications resulting from treatment by a physician or surgeon (Dorland's 29th ed).) The iatrogenic risks of this regimen include: decreased bone density associated with a high risk of osteoporosis, loss of IQ and spatial memory that is not reversible, increased anxiety (seen in animal models (Biggs 2022 pg 11, 12)), and brain development (Bangalore Krishna 2019 pg 365) and fertility risks (Hembree 2017 pg 3880, Bangalore Krishna 2019 pg 365, WPATH 2022 16.1-16.), including permanent sterility (Harris 2020 pg 2454). The most severe risks include shortened life span as adults (de Blok 2021) and sterilization. In my professional opinion, the severe risks of this life-long iatrogenic disease state, for a condition with no physical locus within the body (Schwartz 2021, pg 1) are not outweighed by the regimen's unproven benefits (Byng 2019 pg 1, Griffin 2020 pg 5, Biggs 2022 LTE pg 668).

6. The purported benefits of GAC rely upon idiosyncratic views of "gender," which is not a medical term and has no agreed-upon meaning and is not observable in any clinical capacity. Gender has been used to describe social norms of male and female behavior, but it serves no physiologic function. As a result, the literature conflates phrases like gender dysphoria, gender incongruent, gender diverse, transgender, and gender questioning. Only gender dysphoria is a psychiatric diagnosis listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM V). Simply identifying as transgender or any gender minority is not a pathological condition (i.e., it is not caused by or considered to be a disease).

7. Consequently, the GAC medicalized regimen creates actual physical pathology where none exists. Altering the body to such extremes has not been shown by any high-quality study or review of the literature to improve long-term mental health outcomes for vulnerable children and adolescents.[1] There is a well-recognized paucity of studies examining the use of puberty blockers and cross-sex hormones on children under 13.5 to 14 years of age (Hembree 2017 pg 3883), and even fewer studies involving children younger than 12 years of age (Olsen-Kennedy 2019 pg 3). This lack of data itself renders any assertion of GAC's benefits for these children highly speculative at best.

8. It is my professional opinion that children with gender dysphoria, gender incongruence, gender nonconformity, and those who identify as transgender, or any other gender

[1] Byng R, Bewley S (2019) *BMJ* 9;367:i6439 doi:10.1136/bmj.l6439; Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. *PLOS One* Feb 2021 https://doi.org/10.1371/journal.pone.023894;
Abbruzzese E, Levine S, Mason J (2022) The Myth of 'Reliable Research" in Pediatric Gender Medicine: A critical evaluation of the Dutch Studies—and research that has followed. *Journal of Sex and Marital Therapy* https://doi.org/10.1080/0092623X.2022.2150346;
Cass, H. The Cass Review Interim Report Feb. 2022. https://cass.independent-review.uk/publications/interim-report;
National Institute for Health and Care Excellence (2020). Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria. https://cass.independent-review.uk/nice-evidence-reviews;
National Institute for Health and Care Excellence (2020). Evidence Review: gender-affirming horones for children and adolescents with gender dysphoria. https://cass.independent-review.uk/nice-evidence-reviews;
Swedish Agency for Health Technology Assessment and Assessment of Social Services. Gender dysphoria in children and adolescents: an inventory of the literature. A systematic scoping review Dec 20, 2019 https://www.sbu.se/en/publications/sbu-bereder/gender-dysphoria-in-children-and-adolescents;
Pasternack I, Soderstrom I, Saijonkari M, Makela M. Medical Methods in the treatment of gender dysphoria related to gender variations. A systematic review. Helsinki 15.5.2019. www.summaryx.eu;
Council for Choices in Health Care in Finland (COHERE). Medical treatments for gender dysphoria that reduces functional capacity in transgender people-recommendation. 11 June 2020 www.palveluvalikoima.fi/en.

identity, should mature with their functional biological processes intact and without the introduction of iatrogenic risks to their capacity for healthy physiologic functioning, especially reproductive function. Gender dysphoria has no locus anywhere on the physical body, and GAC artificially *creates* a physical pathology where none existed, destroying the right of a child to develop with his or her functional bodily capacity intact. Moreover, because blocking puberty at the earliest signs of pubertal development (called Tanner stage 2) and then administering cross-sex hormones significantly risks future fertility (Klipstein 2020), GAC violates the child's right to an open future in which his or her future reproductive goals can be actualized (Harris 2020 pg 2259).

9. It is also my professional opinion that children and adolescents who undergo the current regimen of GAC do not have the developmental, intellectual, or emotional maturity to assent to the treatments. Nor do their parents have the ability to provide fully informed consent because there are no guidelines regarding fertility preservation for transgender individuals, and this confines the effectiveness of fertility counseling (Choi 2022 pg 10). Studies have shown that discussions surrounding fertility preservation even for children with cancer are underutilized and family satisfaction with the process is lacking (Klipstein 2020 pg 10); this also appears to be the case for fertility preservation counseling for children who are undergoing the medicalized GAC regimen. There are no clear guidelines or standard practices for fertility preservation counseling for transgender youth (Harris 2020 pg 2453). Fertility preservation counseling for transgender-identifying youth reveals varying degrees of understanding amongst parents and guardians (Harris et al. 2020 pg 2456), and less than 5% of transgender adolescents in one study accessed fertility preservation (Pang et al. 2020). Another study has shown that 35.9% of transgender and gender non-conforming adolescents were interested in biological parenthood, but that only 13.5% had

discussed effects of hormones on fertility (Cheng 2019 pg 12). The variance of what children and adolescents express about their future reproductive goals and actually receiving informed discussions about fertility and fertility preservation is very concerning, because it is well documented in the medical literature that potential risks of long-term exposure to hormones confers to the patient (or future offspring) are unknown (Cheng 2019).

10. All these data call into question how well the informed-consent process relays crucial facts about the permanent implications of GAC and the very limited, experimental options for "fertility preservation" available to young children and adolescents who undergo this regimen. There are *no* robust data that address fertility outcomes in these young patients for whom GAC began at Tanner stage 2. It is noted that "prepubertal transgender children may be forced to choose whether they want to experience permanent changes to their body associated with puberty or whether they want to transition and risk irreversible infertility" (Cheng 2019 pg 215). Up to 95% of transgender children undergoing medical treatment could experience permanent sterility (Harris 2020 pg 2462).

11. There are available, non-experimental fertility preservation technologies for use *after* natal pubertal transition is fully complete, and we do have some data regarding female patients who have taken testosterone *after* their female pubertal development was complete (Light et al. 2014). In contrast, the "fertility preservation" options for pre- and early pubertal children are still experimental. There have been only two live births *ever* reported for any female who underwent ovarian tissue cryopreservation prior to onset of menses. As for pre- or early pubertal males, any discussion regarding fertility preservation at Tanner stage 2 of puberty is purely theoretical, as the only data that currently exists regarding the possibility of achieving spermatogenesis from immature spermatogonal stem cells is from animal models (Ainsworth 2020

pg 786). Despite a long history of experimentation with trying to mature sperm from immature human testes cells or testicular tissue, this has not yet been developed in humans (Ibitsham 2020 pg 15). Because the GAC regimen at early pubertal development (Tanner stage 2) will almost certainly result in sterilization (there are no data providing any evidence to the contrary), and because the "fertility preservation" options for these children are inaccessible, experimental, and speculative, it is my opinion that any notion of informed consent to the risks of GAC at Tanner stage 2 is illusory.

12. In the absence of compelling data, the GAC regimen at early pubertal development (Tanner stage 2) constitutes a live experiment that significantly harms the physiologic functional capacity of healthy children and adolescents.

II. Qualifications

13. I received my medical degree from the University of Utah and my residency training in Obstetrics, Gynecology, and Women's Health at the University of Minnesota. I have a Master of Public Health degree from Yale University. I am Board Certified by the American Board of Obstetrics and Gynecology and am a Fellow of the American College of Obstetrics and Gynecology. My practice experience includes multispecialty group practice as well as academia. In addition to clinical care, I teach medical students and medical residents in the specialties of obstetrics and gynecology, family medicine, and emergency medicine.

14. I provide care, including medical and surgical care, for female patients at all areas of the reproductive life span, from early puberty to post-menopausal. My care has included: monitoring for gynecologic malignancies, endometriosis, painful menses (dysmenorrhea), abnormal uterine bleeding, uterine fibroids, endometrial polyps, pre-cancerous lesions of the cervix, menopausal symptoms, ovarian cysts, ovarian masses, infertility, polycystic ovary

syndrome, sexually transmitted infections, females with differences in sex development, and all aspects of pregnancy, birth, and postpartum care, including surgical care for gynecologic or obstetric emergencies. Currently, I concentrate my practice on caring for female patients in the hospitalized setting, providing care in the antepartum, intrapartum, and postpartum periods. I also perform surgical care for female patients with gynecologic or obstetrical emergencies. A significant proportion of the patients for whom I provide care do not have access to a personal physician/clinic for their obstetric or gynecologic care.

III. Medical Organizations Normally Treat Concerns of Sterilization Seriously—But Not When It Comes to Transgender Youth

A. ACOG

15. I have treated patients who identify as transgender in the context of pregnancy and birth. My experiences caring for pregnant patients who identified as transgender led me to seek guidance from the American College of Obstetrics and Gynecology (ACOG), as there is a dearth of literature on this specific subject. I have trusted ACOG since I was a medical student, and much of my practice is based on their clinical guidance. The time I began seeking this information also coincided with the reports from the UK, where the Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Trust was being sued by a young patient named Keira Bell (*Bell and Mrs. A v. The Tavistock and Portman NHS Foundation Trust*, 2020). I had not been aware that minors were allowed to undergo medicalization and surgery to alter their physical bodies in an attempt to provide aesthetic congruence to match the opposite sex. I read an interim board report from June 2015 and learned from the data that natal female patients actually had worse mental health after one year on puberty blockers than at baseline (an increase in the statement "I deliberately think about harming or killing myself") (The Tavistock and Portman

NHS Foundation Trust 2015). This shocked me because the justification for initiating this medicalized pathway was to improve psychological functioning.

16. At this same time, I read the ACOG Committee Opinion number 685, entitled "Care for Transgender Adolescents," which was published in January 2017 and reaffirmed in 2020 (ACOG Committee Opinion No. 685, withdrawn 2021). The document favorably discussed medicalization of transgender minors with gonadotropin releasing hormone agonists (GnRHa) and supraphysiologic doses of testosterone, even as it noted that "there is a concern that testosterone may cause future damage to ovaries and, thus, lead to infertility." It also recommended invasive, irreversible procedures such as bilateral mastectomies (which the document called "top surgery") and other procedures (labeled "bottom surgeries"), such as hysterectomies (removal of the uterus), oophorectomies (removal of the ovaries), and phalloplasties (the surgical creation of the facsimile of a penis from skin and soft tissue removed from either the forearm or the thigh of a female patient). (ACOG Committee Opinion No. 685, withdrawn 2021). ACOG's recommendation of these serious, life-altering procedures seemed to me to be at variance with the vast majority of ACOG documents published on surgical interventions, which recommend caution and safeguarding, especially in regard to fertility preservation in minors. As an example, a gynecologic pathologic condition with known physical locus is endometriosis, which is known to be the leading cause of secondary dysmenorrhea (pain during menstrual periods) in adolescents. According to ACOG, the goals of therapy for this condition include symptom relief, suppression of disease progression, and *protection* of future fertility, with the committee opinion specifically stating that "adolescents with endometriosis should not be treated with oophorectomy [removal of the ovaries] or hysterectomy [removal of the uterus]." (ACOG Committee Opinion No. 760, reaffirmed 2021).

17. ACOG has written extensively about the harms of medical abuse in the form of coercion and sterilization of vulnerable women. It was therefore alarming to read about the treatment of adolescents who identify as transgender involving invasive and often irreversible sterilizing interventions for a condition that does not carry a medical diagnosis. (The document did not mention gender dysphoria, and identifying as transgender is not a pathological condition.) The ACOG Committee Opinion "Sterilization of Women: Ethical Issues and Consideration" expressly and strongly cautions against treating sterilization lightly: "The suggestion that few protections are needed has been met with deep concern from many reproductive justice advocates, who remain worried about the potential for sterilization abuse of low-income women, women of color, or other disadvantaged women." (ACOG Committee Opinion No. 695, reaffirmed 2020). The opinion also emphasizes that full cognitive maturation, including the capacity to incorporate long-term goals into complex decisionmaking, is not reached until the mid-20s. Importantly, the opinion highlights concerns with the counseling process for *adult* women seeking permanent sterilization.

18. There is an egregious history in the United States of sterilizations being performed on disadvantaged and vulnerable women, and the counseling procedures for this intervention have been called into question. As recently as 2006-2010, 140 incarcerated women in California were sterilized; many of the women reported significant pressure from prison and hospital medical personnel to undergo the sterilization procedure (ACOG Committee Opinion No. 695, reaffirmed 2020).This occurred even *after* the US Department of Health, Education, and Welfare developed protective regulations in 1976 for Medicaid-funded women to prevent further coercive or non-consensual procedures by *prohibiting the sterilization of women younger than 21 years old* and of women with a mental disability. The regulations also required waiting periods before the consent is obtained and the procedure performed (ACOG Committee Opinion No. 695, reaffirmed 2020).

19. It is well established that sterilization for a woman under 30 years of age leads to a 20.3% probability of regret (measured to 14 years from the procedure), compared to a rate of 5.9% for women who are 30 or older when they are sterilized (ACOG Practice Bulletin No. 208, 2019). Women under age 30 are also up to 8 times more likely to undergo procedures to try to reverse sterilization compared to women 30 and older (ACOG Committee Opinion No. 695, reaffirmed 2020). The likelihood that women sterilized between the ages of 18-24 will request sterilization reversal is 40.4%. Males who undergo vasectomy at young ages are also more likely to have the procedure reversed than those who had the procedure performed at older ages (ACOG Practice Bulletin No. 208, 2019). These documents from ACOG do not even mention sterilization in anyone under 18 because it is uniformly not recommended in every clinical scenario—except, it now seemed, when it pertained to adolescents who identified as transgender.

20. Because of the stark contrasts between the Committee Opinion 685 and the other ACOG documents recommending safeguards around the procedure of sterilization, I communicated my concerns to ACOG Clinical members about this document in January 2021. On February 6, 2021, I submitted to ACOG the Board Papers from the Tavistock and Portman NHS trust from 2015, which on page 53 reveals the data that the mental health of young female adolescents worsened after administration of GnRHa. In March 2021, the ACOG Committee Opinion 685 document was withdrawn and replaced with a new one, Committee Opinion 823, "Health Care for Transgender and Gender Diverse Individuals," (ACOG Committee Opinion No. 823, 2021) which does not specifically address patients still in the developmental phase of adolescence.

B. WPATH and Endocrine Society

21. After this experience, I began to read the evidence base for gender affirming care to treat gender dysphoria in minors. The studies done by the Dutch and the British had used chronological age (minimum of age 12) to determine when to use puberty blockers (de Vries 2011 pg 2278, Table 1; Carmichael 2021), rather than stages of pubertal development. However, in 2017, the Endocrine Society issued guidelines to use Tanner stage 2 of pubertal development, rather than chronological age, as the determining factor to start puberty blockers (Hembree et al. 2017 section 2.2). The World Professional Association for Transgender Health (WPATH) standards of care (SOC 7) also recommended young people could start puberty blockers after they had reached at least Tanner stage 2 of pubertal development (WPATH 2012). The current WPATH guidelines, SOC 8, have *no* minimum age limit for hormonal or surgical interventions to transition a minor.

22. The shift from using chronological age (an average of 13 years in the Amsterdam Clinic study and 12 years in the Tavistock study) to Tanner stage 2 of pubertal development to time GnRHa administration concerned me because the gametes of both males and females are not fully mature at Tanner stage 2 of physiologic development. That means that the discussion about "fertility preservation" is largely academic, not a clinical reality, because the technological capacity for maturing gametes from a child or young adolescent at Tanner stage 2 is only available in experimental, highly specialized onco-fertility centers for females, and it has not been demonstrated in males outside of animal models.

23. Tanner stage 2 is when breast buds start to develop in females and when slight scrotal enlargement occurs in males; this can occur as young as age 8 in female children and 9 in male children (Olson-Kennedy et al. 2019). Gametes are usually mature (termed spermarche in

males and menarche in females, for whom the phase of development is manifested by menstruation) by Tanner stage 4 of clinical pubertal development (Emmanuel and Bokor 2022). Use of Tanner stage 2 belies the frequent claim that "children (as opposed to adolescents) are not treated with puberty blockers"; the American Academy of Pediatrics defines childhood as ages of 2-12 years. (Hardin et al. 2017).

24. Moreover, while puberty blockers are oft-cited as merely a "pause button," in clinical practice they seem to be a gateway to cross-sex hormone use by crystallizing gender dysphoria as a first step on a cascade of interventions (Griffin et al. 2020 pg 5), with suppression of puberty becoming a "self-fulfilling prophecy" (Biggs 2022 pg 5). This is also reflected in the data from the Dutch clinicians, as well as the experience of the Tavistock clinic in London. (Biggs 2022 pg. 5). Yet WPATH advocates beginning to transition 8 or 9 year-old children at the first signs of puberty, and the current WPATH document has no age limits to when medicalized or even surgical intervention might be able to occur.

IV. Biological Development: A Necessary Underpinning for Understanding How Fertility Preservation Techniques Work

25. Gender does not exist in the body or in any bodily structure or process; it is not assigned at birth. The phrase "gender assigned at birth" is a misnomer. This is in contrast to sex, which has observable characteristics that can readily be observed. The external phenotype correlates over 99.98% of the time with the individual's internal reproductive pathways and gametes (Sax 2002). What this means is a newborn infant observed to have a penis and scrotum is male; if there is a vulva, the baby is female. A physician is not needed to "assign" the sex of a newborn child; mothers easily observe the sex of their children at birth and have done so for centuries, before the medical establishment inserted itself into the birth process. Very rarely, there are differences in sex development observed; in such rare cases, the sex can generally be known

with use of chromosomal analysis and non-invasive imaging procedures. It is important to understand that individuals who are diagnosed with differences in sex development are still determined to be female sex or male sex.

26. The following discussion conveys the facts of human development and physiologic processes which are undermined at key pathways of healthy bodily function when the current regimen of GAC is administered at Tanner stage 2 of pubertal development. It is necessary to review physiologic development in order to explain how disruptions in this process by GnRHa and supraphysiologic exogenous sex steroid administration leads to a disease state[2] in the developing juvenile human in nearly every organ system, including the reproductive system, where it renders the juvenile human sterile. Especially for children younger than 12 (Olson-Kennedy et al 2019) there is a dearth of research (Mahfouda et al 2017) to inform evidence-based practice for use of puberty suppression; as such, this practice remains experimental.

27. *First*, I will discuss embryonic development and the process of sex differentiation. *Second*, I will discuss normal childhood and pubertal development and how the use of GnRHa as well as supraphysiologic hormone administration disrupts healthy biological processes by inducing a disease state in these children and adolescents. *Third*, I will discuss the realities about fertility preservation techniques and the significant limitations to implementation and practice. *Fourth*, I will respond to the claims made by Plaintiffs' experts. *Last*, I will discuss how attempts to represent GAC as the "standard of care" (Coleman et al. 2022) are disingenuous since GAC is based on poor evidence, violates a minor's right to an open future with reproductive potential, and constitutes a live experiment on vulnerable children and adolescents who are diagnosed with

[2] Disease is defined as any deviation from or interruption of the normal structure or function of a part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown. (Dorland's 29th ed.)

gender dysphoria or otherwise identify as gender incongruent, gender non-conforming, transgender, nonbinary, or another gender minority.

A. Embryonic Development

28. Humans belong to the mammalian clade of the animal kingdom. Mammals reproduce sexually by internal fertilization and give birth to living progeny which use mammary glands for nutrition. The organization of mammalian species is divided between those with sessile, large gametes (female) and small mobile gametes (male). Reproduction in mammals is binary.

29. In order to generate a human embryo, fertilization must occur. Fertilization is the process by which a haploid (i.e., containing one set of unpaired chromosomes) female gamete (ovum, 23 X) is fused with a single male gamete (spermatozoan, 23 X or 23 Y); the two gametes exchange genetic material to restore the diploid (or complete, 46 XX or 46 XY) set of chromosomes, half from the male and half from the female. If this is successful, the fertilized ovum will undergo a series of divisions, the first of which is the zygote. The zygote contains its own unique combination of genetic material in equal parts from each parent; it is unique. It has the genetic potential for further development into a live birth so long as the combination is compatible with development into the zygotic stage and the later processes of embryonic and fetal development are not disrupted.

30. A series of mitotic divisions ("mitosis" is the division of one cell into two cells with the same genetic components) in the successfully created zygote continues to occur, and is now called a blastocyst. The multi-cellular blastocyst travels from the fallopian tube into the uterine cavity where it is able to implant. Implantation into the uterine cavity occurs approximately 6-12 days post fertilization. If any developmental process prevents implantation, the mammalian human embryo will not be able to survive and will cease to develop.

31. If the blastocyst implants successfully, further developmental processes of the embryo can continue—provided no interruption occurs. This period of embryonic development is known as organogenesis. In this stage of development, all the "blueprints" from the primordial germ cells have the potential to create the developmental pathways from which all organ systems develop.

32. Sex differentiation occurs during organogenesis. This process starts with germ cell migration. The germ cells that will differentiate into the gametes are found in the primitive endoderm within the yolk sac of the human embryo beginning at the 3rd week post fertilization. An embryo with the XX sex chromosome complement is female, and those with XY are male; this is determined at conception. The germ cells migrate along the dorsal mesentery of the hindgut arriving at the primitive gonads at the 5th week and invade the genital ridges in the 6th week of development (Langman's Embryology 8th ed 2000, Lippincott; Langman's Embryology 15th ed 2024, Wolters-Kluwer).

33. If the germ cells do not arrive at the site of the gonadal ridge, the gonads will not develop. These germ cells are the direct precursors to the gametes (spermatogonia in the genetic male embryo and the oogonia in the genetic female embryo). The gametes are unique from the rest of the somatic (body) cells, because they undergo a specialized type of cell division called "meiosis."

34. Meiosis is an intricately timed process and is unique to male and female gametes because the process allows the chromosomes from each parent to combine and generate a new human zygote once the developmental process of sexual maturity is reached. The function of this process is to ensure propagation of the species. In the female, the process of gametes undergoing meiosis starts well before birth; in the male, the gametes do not enter meiosis until the pubertal

transition. As I will detail in later sections, this process has extremely important implications for fertility and fertility preservation in both females and males.

1. Female Sex Developmental Pathway

35. Once the germ cells reach the gonad of the genetic female, they have an inductive influence on the development of the gonad into the ovary. The surface epithelium of the ovary continues to proliferate and penetrate the mesenchyme, and will eventually surround one or more germ cells. The germ cells will differentiate into oogonia, and the epithelial cells will become the follicular cells. By the end of the 3rd month post fertilization, the oogonia are arranged in clusters surrounded by a single layer of flat epithelial cells. The majority of the oogonia germ cells continue to divide by mitosis, but some will undergo meiosis.

36. By the end of the 7th month, nearly all of the oogonia that have entered meiosis have undergone natural degradation (atresia) except for a few near the ovary surface. The oogonia which start the process of meiosis are called the primary oocytes and are considered to be in meiosis prophase 1. The primary oocyte, surrounded by the flat epithelial cells, is called the primordial follicle.

37. Near the time of birth, the primary oocytes' DNA is "arrested" in a phase of meiosis prophase 1 known as "diplotene." The granulosa (follicular) cells surrounding the oocyte keep the oocyte in this arrested development phase until puberty by secreting a small protein called oocyte maturation inhibitor.

38. Once in the diplotene stage, the primary oocytes enter a long period of resting/quiescence before and beyond birth. The total number of primary oocytes present at birth are approximately 600,000-800,000. Approximately half of these primary oocytes are lost due to natural degeneration during childhood, leading to approximately 400,000 remaining at the start of

puberty. Only a small percentage of primary oocytes will be ovulated during the female's reproductive lifetime (Langman's 2000, 2024).

39. In females, primary oocytes have already started the process of meiosis (which is then arrested up until puberty) before birth; thus, they are *potentially* capable of maturation. Importantly, the surrounding follicular cells of the primary oocyte—which are essential for fertility—do not mature *until* the pubertal transition when menarche (also called menstruation) occurs. These facts have implications for fertility preservation techniques, which I will describe later in the report.

40. In the absence of the Y chromosome, the development of the female internal ductal development and external urogenital system continues into fetal development. By the beginning of the 4th month post fertilization, the Mullerian, (also called paramesonephric) internal ductal system (the uterus, fallopian tubes, cervix, and upper third of the vagina) are complete. By 20 weeks post fertilization the external labia, clitoris, and lower portion of the vagina are developed from the urogenital sinus, as is the vulva, which is observed at birth.

2. Male Sex Developmental Pathway

41. Embryos with XY chromosome complements have a similar timeline of sexual differentiation during the period of organogenesis, with a few key differences.

42. The germ cells invading the gonadal ridge will develop into testes if the SRY (testis determining factor) is present on the short arm of the Y chromosome. The gene product of the SRY gene is a transcription factor that helps express genes that encode for a protein called "MIS," or Mullerian inhibitory substance (also referred to as "anti-Mullerian hormone" or AMH), as well as the hormone testosterone (Langmans 2000, 2024). Cells supporting the germ cells in the male embryo are developed from the adjacent mesenchymal and epithelial cells. Fetal *Leydig* cells develop from the mesenchyme and the *Sertoli* cells develop from the surface epithelium. The

Leydig and Sertoli cells are very important for the development of the male in many ways. They ensure testosterone is present locally during the organogenesis of the genitourinary system in the male, and provide nutrition and support for the immature germ cells that will eventually become sperm in the male adult.

43. The fetal Leydig cells begin to secrete testosterone at eight weeks of embryonic development. The Sertoli cells secrete a hormone called androgen binding hormone. Testosterone in its active form, dihydrotestosterone, is required for the virilization of the external male genitalia (scrotum and penis). Localized testosterone produced by fetal Leydig cells as early as 8 weeks ensures virilization will continue throughout in utero development.

44. The sertoli cells secrete mullerian inhibitory substance (MIS), also known as anti-mullerian hormone (AMH). MIS/AMH hormone causes the regression of the paramesonephric ducts, meaning the female internal reproductive organs do not develop in the male embryo. The mesonephric ducts will then develop into the ducts that comprise the vas deferens and epididymis.[3]

45. The germ cells that migrate to the genital ridge in the male embryo become spermatogonia. They are present at birth in their immature form and will remain immature until puberty occurs. That is, they have not yet started the unique cellular division known as meiosis. This is in contrast to the oocytes in the female, which have already started the early stages of the part of cellular division called meiosis and are arrested at this developmental phase until ovulation occurs at puberty. Unlike the oocytes, the spermatogonia still must undergo a series of mitotic divisions before they are ready to undergo meiosis and thus before they are mature. The maturation of the diploid spermatogonia into the haploid mature spermatozoa is a very complex process and

[3] There are very rare genetic conditions in which there is incomplete expression of these genes responsible for sexual differentiation, but these children still develop along the male or female pathway depending on other factors important for the differentiation of the urogenital system.

it can only be confirmed with certainty to have occurred during male puberty at the period of spermarche. Spermarche is the male corollary to menarche in the female. These processes occur in late pubertal development, usually at Tanner stage 4 (Emmanuel & Bokor 2022). ***Thus, at Tanner stage 2 in the male, gametes are still not mature***. This fact has extremely important implications for fertility and fertility preservation, as discussed later in this report.

B. Childhood and Pubertal Transition

46. In the previous section, I outlined the embryonic developmental stages of development as it pertains to sexual differentiation in the male and female embryo, continuing into the fetal developmental stage. Once the fetus has delivered and is now in extrauterine life (i.e., is outside the uterus), further growth of the neonate into infancy, childhood, and during the pubertal transition is also susceptible to disruptions in physiological processes which can harm the developing human.

47. Once the separation from the maternal and placental estrogen and progesterone occurs at birth, the baby experiences a sudden decrease in maternal hormones. This sudden loss of the maternal hormones will prompt the hypothalamus of the baby to release GnRH. GnRH will cause the pituitary gland to release Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH). These hormones will then cause the ovaries in the female baby to produce estradiol; in the male baby, these hormones will cause the testes to produce testosterone. The result of this process is a very short period of estradiol increase in the female infant and testosterone increase in the male infant. This transient rise in estradiol and testosterone in infants rapidly signals back to the hypothalamus in the brain to stop release of FSH/LH; that, in turn, reduces the estradiol (in the female) and testosterone (in the male) to very low levels until about 6-8 years in childhood. This period is not well understood but is postulated to 'set' the hypothalamic/pituitary/gonadal

communication that is important for later pubertal transition (Speroff & Fritz 2005). Once nighttime pulsatile secretion of GnRH starts to occur between ages 8-13 in females and 9-14 in males, the very earliest pubertal transition has begun.

48. Gonadotropin Releasing Hormone (GnRH) is a small protein hormone. It is known as a neurohormone because it is made in the part of the brain called the hypothalamus, connecting it to the hormone gland called the pituitary by a delicate network of blood vessels called the hypophyseal circulation. When GnRH is released by the hypothalamus, it lasts only 4-8 minutes before it undergoes degradation (its half-life is 2-4 minutes). Because of GnRH's short half-life and dilutional effects that the circulation has on GnRH's concentration once released, control of the reproductive cycle depends on a constant release of GnRH. To achieve this, the arcuate nucleus of the hypothalamus releases GnRH in a pulsatile fashion, the critical range of GnRH in the circulation being very narrow.

49. Once out in the hypophyseal circulation, GnRH reaches the anterior pituitary gland and binds to cells in the pituitary called gonadotropes. The immediate effect of this binding is the release of LH and FSH from the gonadotrope cells. LH and FSH are also released in a pulsatile fashion just like GnRH.

50. Once at the level of the ovary, the LH and FSH hormones (also referred to as gonadotropins) act on the Theca and Granulosa cells respectively, which are cells supporting the primary oocytes in the female ovary. At the level of the testes, gonadotropins act on the Leydig and Sertoli cells supporting the male immature spermatogonia. In females, these hormones cause the release of estradiol. In males, these hormones cause the release of testosterone. During early puberty, the communication between the hypothalamus, pituitary, and gonads starts to develop and mature; this process takes several years during pubertal transition.

51. Recall that primordial follicles in the human ovary are present before birth and consist of an oocyte ("arrested" in the diplotene stage of meiosis I) and a single layer of flat granulosa cells which support the oocyte. Primordial follicles that number in the millions during mid-gestation naturally reduce to approximately 400,000 at the beginning of puberty. The primordial follicles are in a consistent state of turnover and natural cell death called apoptosis, which continues throughout the entire lifespan of the female.

52. Once early pulsatile release of FSH occurs during puberty, the follicle destined to ovulate is "rescued" from natural cell death; the "fate" of the primordial follicle is apoptosis (natural cell death) unless it is able to be "rescued" from this natural process with the increase in FSH during puberty. The mechanism determining which primordial follicles will be "rescued," and thus progress to become the dominant follicle destined for ovulation, is not known. It is postulated that the follicle is "singled out" for this process by a combination of "readiness" in the microenvironment of the ovary, and appropriate levels of increased FSH in circulation (Speroff and Fritz, 2005).

53. The primordial follicle that first responds to the FSH "signal" to grow is the follicle destined to ovulate. In this process, the oocyte increases in size, and the granulosa cells surrounding the primary oocyte change from flat to cuboidal and increase in number. Intricate channels called gap junctions begin to develop between the granulosa cells and the oocyte. These gap junctions are very important, because they allow nutrients and molecular signals to "pass," which help grow and sustain the oocyte as well as mature the granulosa cells. The continued growth of the oocyte and the maturation of the granulosa cells are dependent upon the signals between these cells.

54. Under continued influence of FSH, the dominant follicle becomes surrounded by the fluid present in the spaces between the granulosa cells, and a fluid-filled cavity forms. The

granulosa cells surrounding the oocyte within this cavity are called the cumulus oophorus. The theca cells are adjacent to the granulosa cells in the ovary. The FSH receptors on the granulosa cells, and the LH receptors on the theca cells, allow these cells to respond to these hormones. The theca cells secrete androstenedione and testosterone (from the precursor cholesterol) which is then aromatized to estradiol by the granulosa cells. The amount of estradiol produced is dependent on the number of FSH receptors on the granulosa cells. Uterine blood flow rises sharply with elevated estrogens during this phase, providing evidence of a physiological role of estrogens in vasodilation, which help sustain the pregnancy if fertilization occurs by providing a physiologic mechanism by which the pregnancy receives adequate oxygenation and nutrition from placental circulation (Li Y et al 2021, Bai J et al 2020).

55. The increase in estradiol from the granulosa cells in response to FSH ultimately causes a large increase in LH several hours before the dominant follicle undergoes ovulation. The estradiol and progesterone levels are at their peak at this time (progesterone is secreted by the corpus luteum in the ovary), and organize the endometrium to prepare for pregnancy. If fertilization does not occur, the corpus luteum will fail to be "rescued" from programmed cells death, which in turn causes estrogen and progesterone levels to fall; uterine lining is then shed in response to the progesterone withdrawal, and the shedding of the endometrial lining of the uterus that ensues is recognized as menstruation. ***Notably, the maturation of the supporting follicular cells to create the cumulus oophorus, and thus the dominant follicle that is capable of being ovulated, only occurs during puberty.***

56. In males, the gametes themselves can mature only with puberty because the germ cells have not yet entered the cellular division of meiosis (unlike the primary oocytes); this process is dependent on LH and FSH release after GnRH signals the Leydig and Sertoli cells to mature the

spermatogonia into primary spermatocytes. Type A spermatogonia undergo mitosis and become primary spermatocytes; after a prolonged prophase of about 22 days, these cells will then enter, and rapidly complete, meiosis I and form secondary spermatocytes. Secondary spermatocytes complete meiosis II and form spermatids. Spermatids are now haploid and able to undergo spermiogenesis and mature spermatozoa. These mature spermatozoa enter the lumen of the seminiferous tubules and gain motility in the epididymis. The process of maturing a spermatogonia into a spermatozoan takes approximately 64 days.

57. In general, the first sign of puberty is an acceleration of growth followed by either breast budding (thelarche) in females or increase in scrotal size in males. Sometimes adrenarche (axillary and pubic hair) occurs prior to breast budding but often occurs two years after thelarche. Menarche (the onset of the shedding of the endometrial lining, or menstruation) is a late event in the pubertal transition in females, occurring after the peak of growth has passed—2 years on average after thelarche when breast development is Tanner stage 4. In the United States, the average age of menarche has been 12 years for over three decades.

58. Spermarche in males is the equivalent of menarche in females and occurs at Tanner stage 4 of physical pubertal development (Emmanuel and Bokor 2022). Tanner stage 2 of pubertal development occurs as early as age 8 in female children and age 9 in male children (Olson-Kennedy et al. 2019). The American Academy of Pediatrics defines childhood as between 2 and 12 years of age (Hardin et al. 2017).

V. Effects of Puberty Blockers on the Developing Child and Young Adolescent

59. The mechanism of action of GnRH agonists—"puberty blockers"—ultimately prevents the release of gonadotropin hormones LH and FSH from the pituitary gland, when administered continuously. This action prevents these hormones from acting in the ovaries in

females and the testes in males, ultimately preventing the release of estradiol and testosterone, respectively. ***If administered at Tanner stage 2, before gametes are mature, continuous administration of GnRHa makes the full maturation of the gametes impossible***.

60. A concern with the use of puberty blockers in female children before menstruation has begun is the fact that the menstrual cycle can be used as a "vital sign," and aberrations to the cycle can be a sign of underlying physiologic disease (ACOG Committee Opinion 651, reaffirmed 2020).This shows that there are other consequences to the healthy physiological development of female children when menstrual cycles are stopped before they even begin.[4]

61. There are also potential risks to children and young adolescents who have differences of sex development (DSD, also referred to by many as intersex) who receive GnRHa drugs. Such drugs can mask conditions that sometimes are diagnosed only during the pubertal transition.

62. GnRHa are used at times to alleviate symptoms due to physical gynecologic conditions in female adults, such as endometriosis and uterine myomas. Risks of GnRHa in adult females include hot flushes, headache, mood changes, vaginal dryness, joint and muscle stiffness, depression, and bone loss (Speroff & Fritz 2005). These same risks and side effects are present in a child taking this drug, in addition to other known and unknown risks.

63. Adult females using this medication for the aforementioned conditions are limited to 6 months duration of treatment. Importantly, during treatment with GnRHa adult women are prescribed either estrogen or progestogen (or both) to "add back" what the GnRHa medication has caused their body to stop producing physiologically. This "add back" hormone therapy is used to

[4] "It is imperative to communicate with patients and their caregivers the need for the first menstrual period as an indicator of typical pubertal development." (ACOG Clinical Consensus No 3 Sept 2022: General Approaches to Medical Management of Menstrual Suppression, pg 536.)

prevent cortical bone loss, for instance. The amount of bioavailable estrogen circulating in the blood is the most consistent predictor of bone density in men and women (Speroff and Fritz 2005, pg 369). Children receiving GnRHa for gender affirming care at Tanner stage 2 can potentially go years without receiving any hormonal support during the only time in their lives in which cortical bone mass would otherwise be maximized during physiologic development. Thus, this group of children is especially vulnerable to long term deficits in bone health, and knowledge gaps remain for this cohort (Klink 2015 pg 274).

64. While puberty blockers are often described as a "pause" that can be stopped at any time, in clinical practice, nearly all adolescents (98%) who begin GnRHa as part of gender-affirming care will go on to be prescribed cross-sex hormones (Carmichael 2021; de Vries 2011; Biggs 2022).

65. ***This pathway is significant because when the administration of GnRHa arrests gametes in normal pubertal development at Tanner stage 2, and then high-dose cross-sex hormones are administered (without a gap between administration of the GnRHa and cross-sex hormones), then, based on what we know of physiological development, there is no way for the gametes to ever mature***. In other words, if a child begins puberty blockers at Tanner stage 2, as recommended by WPATH and the Endocrine Society, and then moves on to cross-sex hormones without a gap in "care," he or she can risk permanent sterility.

66. Authors of several papers have indicated that the GAC regimen when initiated at Tanner stage 2 of puberty will lead to permanent sterility (Harris 2019; de Nie 2022). Regarding male children specifically, de Nie states on p. 298: "A complicating factor for contemporary fertility preservation in transgender female [i.e., natal male] adolescents is the requirement of complete spermatogenesis, which only develops from Tanner 3 onwards. ***If puberty suppression***

is started in Tanner stage 2, full spermatogenesis is usually not present yet and therefore preservation of spermatozoa is not possible." (Emphasis added.)

67. In females who identify as transgender men, there are isolated reports in the literature of adults who have carried pregnancies and given birth (Light et al. 2014); however, the regimen they received is not well known (Moravek et al. 2020). There are no fertility data I am aware of for females who received GnRHa at Tanner stage 2 of puberty, followed by cross sex hormones.

VI. Effects of Supraphysiologic Doses of Testosterone in Females

68. Total testosterone levels in reproductive age females typically range between 20-80 ng/dL (Speroff and Fritz, 2005). There are medical conditions in which the testosterone levels are higher than physiologic values. The most common condition of hyperandrogenism is a poorly understood condition called polycystic ovary syndrome (PCOS) (ACOG Practice Bulletin No. 194, 2018).

69. PCOS is a complex disorder characterized by hirsutism/hyperandrogenism, insulin resistance, and ovulatory dysfunction (most often clinically recognized as irregular periods of uterine bleeding due to the absence of ovulation, or even amenorrhea (the absence of menstruation, and infertility)). The etiology of this condition is unknown, and there is no universally accepted definition. Diagnostic criteria for this condition are not universally agreed upon, leading to varying reports of prevalence. Approximately 5-20% of the female population may have this condition (Liu et al. 2020). An elevated testosterone level is not required to make the diagnosis, only clinical evidence of hyperandrogenism (e.g., male-patterned hair growth, male pattern hair loss, and acne). The hyperpigmented, velvety appearance of the skin called acanthosis nigricans is due to hyperinsulinemia but is often seen in patients with androgen excess such as PCOS.

70. In adult women, PCOS has the potential to cause increased risks of impaired glucose tolerance, sleep apnea, mood disturbances, depression, increased risk of type 2 diabetes, dyslipidemia, non-alcoholic fatty liver disease, visceral obesity, cardiovascular disease, and increased risks for endometrial cancer (ACOG PCOS 2018, Liu et al 2020). The exact pathogenesis of PCOS has yet to be elucidated.

71. PCOS is not typically diagnosed in adolescence due to the immature hypothalamic-pituitary-gonadal axis and risk for over diagnosis. Administration of puberty blockers to young female adolescents or children for years, followed by cross-sex hormones, will mask the clinical diagnosis of PCOS in young females who may be at greater risk of this complex disease. Masking PCOS has deleterious effects because patients need to be closely medically monitored to avoid serious risks to their health.[5]

72. It has been postulated that gender incongruence may be elevated in females with PCOS (Liu et al. 2020) as well as reporting PCOS being more common in female transgender men (Moravek 2018). If PCOS is in fact more common in females who identify as transgender men, and these females already possess increased health risks baseline before starting exogenous

[5] It is recommended to avoid diagnosing PCOS in adolescents until at least 2-3 years post menarche (Goodman 2015 pg 1297). ACOG also encourages caution assigning the diagnosis prematurely (ACOG Committee Opinion No. 789). Even for female adolescents who use estrogen/progestin- or progestin-only hormonal management for dysmenorrhea or contraception, it is still a concern that the hormonal medication could hamper identification of menstrual patterns that, in turn, may delay potential health concerns for adulthood (although hormonal management has endometrial protective effects, reducing risk of endometrial hyperplasia and subsequent atypia, which decreases risk of endometrial cancer). Blocking puberty also poses potential significant risks to girls with differences in sex development who are not diagnosed until adolescence. The GAC regimen confers no such beneficial effects to the endometrium and may in fact exacerbate existing risk factors for endometrial hyperplasia/atypica/cancer with the increased aromatization of testosterone to estrogen.

testosterone administration, their health is placed at even greater risk by masking the effects of PCOS.

73. There are other conditions that cause hyperandrogenism in females. Affecting less than 1-2% of females, these conditions include congenital adrenal hyperplasia, androgen secreting ovarian or adrenal tumors, acromegaly, and Cushing's disease (a condition in which an adenoma called a corticotroph secretes the hormone ACTH which results in an excess of adrenal androgens and cortisol). The level of testosterone in these severely hyperandrogenic disease states can range from 100-300 ng/dL or more.

74. Excess androgens (including testosterone) in females is a serious risk to the healthy functioning of physiologic processes within the cardiovascular, endocrine, neurologic, pulmonary, and reproductive organ systems. Disease states can be caused by endogenous testosterone at levels orders of magnitude ***lower*** than the doses of exogenous testosterone administration in female sex individuals undergoing gender affirming care. The risks to the female body present within the conditions of endogenous hyperandrogenism would also be present in the healthy child or adolescent receiving supraphysiologic doses of exogenous testosterone (such as through gender affirming care). Numerous studies document that endogenously produced androgens leading to hyperandrogenism can contribute to significant health risks (Dubey et al. 2021, ACOG Practice Bulletin No. 194, 2018).

75. Gender affirming care suggests doses of exogenous testosterone in the female to match the normal physiologic male range (typically 320-1000 ng/dL) (ACOG Committee Opinion 823, 2021). These are ***extremely*** elevated androgen levels, the likes of which are not usually seen naturally except in cases of rare androgen-secreting tumors that comprise only about 1% of all

ovarian tumors. When diagnosed, such tumors are promptly surgically removed so that patients are not subjected to years of hyperandrogenism, which carries significant health risks.

76. Data are just now emerging with regard to the iatrogenic physiologic pathology that exogenous, supraphysiologic testosterone administration has to bodily function in females. There is growing evidence that this dose of "maintenance" testosterone therapy increases the risks of myocardial infarction in females who identify as transgender men compared to females who do not take exogenous testosterone (Aranda et al. 2021). A new study presented at the American College of Cardiology's Annual Scientific Session reported a substantially increased risk of serious cardiac events, including stroke, heart attack, and pulmonary embolism in individuals with gender dysphoria receiving GAC with supraphysiologic doses of estrogen or testosterone (American College of Cardiology News Release 2023). Androgens also appear to induce unfavorable responses in the female vascular system which can lead to endothelial dysfunction and mild hypertension; these responses persist as long as the female individual continues to take exogenous testosterone (Stone & Stachenfeld 2020). Endothelial dysfunction precedes clinically detectable atherosclerotic plaques, and it is important to be able to monitor this in females who are taking exogenous testosterone at young ages when their overall risk of cardiovascular events is still low (Gulanski et al 2020 pg 139). Flow mediated vasodilation in the brachial artery was monitored in females who were being administered exogenous testosterone at supraphysiologic female levels in order to affirm physical congruence to the opposite sex; it was found that, compared to females who did not receive these doses of testosterone, the magnitude of the vasodilatory response was attenuated in females who identified as transgender men. This study represents the first time physiological testosterone during testosterone administration for gender affirmation (a range of total testosterone of physiologic male levels in a female) impaired

endothelial function. This is in direct contrast to the effects that estrogen would have in a young female, as endogenous estrogen has beneficial effects, promoting vasodilation and endothelial cell growth and decreasing the development of atherosclerosis. This study directly demonstrates the detrimental effects of androgens on the female cardiovascular system when administered in such exogenously elevated doses to achieve levels more common with male sex.

77. High triglyceride levels appear to be a stronger predictor of increased cardiac risk in females compared to males. Non-HDL (total cholesterol minus HDL–or high-density lipoprotein) and also the ratio of total cholesterol/HDL are predictors of cardiovascular risk in females (Sallam & Watson 2013). In addition to decreased HDL and increased LDL (low density lipoprotein), testosterone administration in female transmen increases BMI and hypertension, with varying effects to triglyceride levels (Velho et al. 2017). All of these risks to the female cardiovascular system are exacerbated by supraphysiologic testosterone administered during gender affirming care. Even among studies which claim that testosterone administered in supraphysiologic doses not increase or exacerbate insulin resistance or markers for cardiovascular risk, such studies are quite small and use blood tests that are not usually measured to diagnose insulin resistance (Chan et al 2018); such findings have not been confirmed with larger studies. In fact, recent emerging data show either elevated cardiovascular risk for individuals who identify as transgender and who are receiving cross-sex estrogen (males) and testosterone (females) (Schutte et al 2022, Nota et al 2019) or inconclusive risk (Masumori et al 2023). These data show that it is too strong to conclude hormones do not "induce risk."

78. The risks of androgen abuse in the form of unmonitored supraphysiologic testosterone administration in females is well documented and includes depression, infertility, and mood instability (ACOG Committee Opinion No. 484, reaffirmed 2021). Testosterone is classified

as a schedule 3 controlled substance, meaning that it is a drug with a moderate to low potential for physical and psychological dependence (ACOG Committee Opinion No. 484, reaffirmed 2021). The psychiatric risks of exogenous testosterone administration are well documented in the medical literature, with higher doses of testosterone associated with hypomanic, manic, or psychotic symptoms (Moravek 2018 pg 694).

79. It has been shown in observational data that there is an increased mortality risk in transgender people using hormone treatment, regardless of type, over the course of five decades (de Blok et al. 2021). The study authors admit that "effects of safety of hormone treatments are scarce, leading to insufficient evidence to determine long-term safety, especially regarding cancer and hormone-sensitive cancers specifically, as well as cardiovascular disease" (De Blok 2021 pg 664).

80. The fertility risks with exogenous supraphysiologic doses of testosterone are not fully known, and there is an acute lack of data disambiguating patients by ages and stages of pubertal development when this drug is administered, noting whether GnRHa were administered prior to treatment, or stating the duration of either or both medications. As one literature reviewer recently wrote: "Unfortunately, in regards to best practices surrounding fertility treatment and/or fertility preservation in transgender men, there seem to be more questions than answers from the available literature… [T]here is a paucity of data directly translatable to the high levels of and prolonged postpubertal exposure to T that is characteristic of gender-affirming hormone therapy. As such, the current status quo is to recommend fertility preservation before initiation of T therapy and, for patients presenting subsequent to T therapy, cessation of T before ovarian stimulation… More clinical outcome data are also desperately needed, however, to ensure we are providing appropriate care to this patient population. The long-term goal should be to equip medical

providers with the information necessary to provide high-quality data-driven counseling regarding fertility options for transgender men" (Moravek et al. 2020 pg 13). This is a remarkable statement because it was written in 2020, years after GAC was widely adopted in the United States without any long-term data—not even animal studies—to help guide best practices. It highlights the medical experimentation being conducted on very vulnerable patients.

81. Further risks to females who undergo GAC with exogenous testosterone include gynecologic malignancies such as endometrial cancer and ovarian tumors, as well as breast cancer. Because prolonged exposure to a hyperandrogenic hormonal environment has been, until the advent of GAC, extremely rare, published information is limited.[6] Most reports are thus case reports. More concerning is the possibility that females who receive GAC are not getting proper healthcare while being put at iatrogenic risk of developing malignancies.

82. There are concerns that the testosterone used in GAC can increase risk of endometrial cancer. Testosterone is known to suppress the hypothalamic-pituitary-ovarian axis, which ultimately prevents estrogen and progesterone synthesis. However, testosterone is also aromatized ("converted") to estrogen. Estrogen, if not balanced with progesterone, will increase the risk of endometrial cancer. A case report of a precancerous lesion of the endometrial lining of the uterus was diagnosed in a young female transgender man at the time of hysterectomy; this is extremely rare in a young patient without any medical comorbidities that contribute to unopposed

[6] ACOG claims "most studies demonstrate that endometrium is atrophic secondary to testosterone use" (ACOG Committee Opinion 823 pg e85) but does not provide any studies demonstrating this to be true. ACOG Clinical Consensus on Menstrual Suppression on pg 536 cites the CO 823 when it again claims: "Although there has been concern for endometrial hyperplasia or malignancy due to aromatization of exogenous testosterone to estrogen with anovulation and therefore chronic unopposed estrogen, this risk is not supported by data. Most studies demonstrate endometrial atrophy with the use of exogenous testosterone as part of a gender-affirming protocol" (pg 536). But this claim does not reference any sources, either.

estrogen. The patient had been administered supraphysiologic testosterone to achieve the range of the male sex (O'Connor et al. 2022).

83. Testosterone administered exogenously induces changes to the ovarian histology similar to PCOS, with an increase in androgen receptors possibly leading to the increased risk of ovarian cancer. Ooophorectomy performed prior to natural menopause also is associated with increased risks of all-cause mortality, dementia, cardiovascular death (Carbonnel et al. 2021, pg 933). Testosterone used for gender affirming care in this population of females makes it difficult to disambiguate these risks, as these data are all for females who have not been exposed to long-term, supraphysiologic doses of exogenous testosterone. Females who identify as transgender often do not access routine gynecologic care, further risking their health (AOCG Committee On Health Care for Underserved Women 2021, Opinion 823).

84. Testosterone administered as part of the regimen in GAC suppresses estrogen production, even though it also gets "converted" to estrogen, which makes it extremely challenging to differentiate the risks to females on this regimen. The decrease in estrogen causes vaginal epithelial cell growth to slow, and the vaginal epithelium becomes thinner and more fragile. This can cause irritation, dryness, and atrophy of the vaginal tissue, which can cause significant discomfort and even bleeding. Critically, estrogen is imperative for the vaginal microenvironment and subsequent health. Estrogen promotes the production of glycogen by vaginal epithelial cells which is a preferred substrate of *Lactobacillus* species of bacteria. Lactobacilli use glycogen to produce lactic acid, which inhibits growth of pathogens such as sexually transmitted infections (*Neisseria gonorrhoeae, Chlamydia trachomatis)* and also bacterial vaginosis. If lactobacilli colonization is impeded, epithelial maturation of the vagina is impaired, which in turn causes

increased susceptibility to other infections such as HIV and HPV. HPV infection is common and is a known risk factor for cervical cancer (Krakowsky et al. 2022).

85. There is also concern for increased risk of breast cancer due to the unopposed estrogen (after aromatization/conversion from supraphysiologic doses of testosterone). One study reported breast cancer in four females who identify as female to male transsexual, two of whom were undergoing masculinizing exogenous supraphysiologic testosterone administration. Two patients developed breast cancer in residual breast tissue 10 years ***after*** breasts had been removed (Trum et al. 2015).

86. In another study, a female adolescent who identified as transgender was prescribed testosterone for under one year and developed a large, borderline malignant ovarian neoplasm, which is very rare in the adolescent population (Millington et al. 2021).

87. To summarize, a growing body of evidence shows females who are administered supraphysiologic doses of exogenous testosterone under the gender affirming care regimen develop an iatrogenic disease state of severe hyperandrogenism, the risks of which are still poorly understood given the duel effects that testosterone has on the female reproductive system (both suppression of estrogen and also conversion to estrogen). This has significant deleterious effects on nearly every female organ system including the associations of risk of certain gynecologic malignancies that are otherwise extremely rare in young, healthy females.

VII. Fertility Preservation Techniques in Gender-Diverse Children Who Undergo GAC at Tanner Stage 2 Are Experimental

88. In both female and male children, fertility-sparing procedures prior to full pubertal development are nascent and considered to be experimental. Currently these procedures are predominantly limited to children who suffer from cancer or other physical disease states that are life threatening and require treatment with chemotherapy, much of which is cytotoxic to gametes.

Because children with cancer do not have the option of waiting to administer chemotherapy (because waiting would introduce unacceptable risk), most often fertility preservation procedures are done in an expedited fashion, very shortly after the child's cancer diagnosis is confirmed. The invasive fertility preservation procedures and techniques are the only intervention available to have a chance of preserving the child's right to an open future in terms of possibly safeguarding their fertility (Klipstein 2020).

89. Pre- or very early pubertal children and adolescents at Tanner stage 2 generally do not have the same options for fertility preservation as those who have fully completed natal pubertal development. The reason for this is that the gametes have not reached maturity if the female has not undergone menstruation or the male has not undergone spermarche (both occur typically at Tanner stage 4 of development). As I will outline below, there are significant limitations with the technological ability to preserve fertility in pre- or early pubertal male and female children for any indication.

A. Fertility Preservation Options for Females

90. For females at Tanner stage 2 of puberty, ovarian tissue cryopreservation exists in theory as an option to preserve fertility, but not in practice for most people (American Society for Reproductive Medicine 2019). With only 2 recorded cases of live births in the world literature in females who underwent ovarian tissue cryopreservation (OTC) prior to the onset of mature gametes (menstruation), this option is extremely limiting in a young female who would otherwise mature to adulthood and perhaps not require any need for fertility preservation at all.

91. The American Society for Reproductive Medicine (ASRM) recently removed the experimental label for ovarian tissue cryopreservation (OTC) in 2019 in their committee opinion regarding fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy

(American Society for Reproductive Medicine 2019). This document subtly broadened the indications for fertility preservation outside of those who have medical conditions that are life threatening, such as malignancy or blood disorders such as thalassemia or sickle cell disease, and for whom treatments are gonadotoxic. The recommendations were made based on the data that OTC has demonstrated success in women achieving 130 live births worldwide with this method as of 2017 (Donnez & Dolmans 3017). The authors acknowledge that the denominator of how many women have undergone OTC is not known, but they report 29%-33% pregnancy rates and live birth rates of 23%-25% from individual centers.

92. Proponents of safeguarding the pediatric population have appealed that this technology should be offered only within the context of institutional review board (IRB) approved research, in order to address the many scientific and clinical questions that are currently unknown in the pediatric patient population (Rowell et al. 2020; Nahata et al. 2020).

93. Currently, most indications for ovarian tissue cryopreservation in females under age 18 are malignant neurological disease, leukemia, sarcomas, and benign hematological disorders (Gjeterud et al. 2021). Most often, ovarian tissue is autotransplanted back into the female patient (Ainsworth et al. 2020) once treatment for the offending condition has been completed and the female has decided she would like to pursue childbearing (provided that the transplanted ovarian tissue is not going to further risk re-introduction of malignancy) (ASRM 2019). It is noted that benign disorders in females under 18 years of age which require treatment with gonadectomy or gonadotoxic agents comprise a growing indication for ovarian tissue cryopreservation in this age group (Gjeterud et al. 2020). However, as the ASRM notes: "efficacy, safety, and reproductive outcomes after ovarian tissue cryopreservation are still limited," and OTC should be offered only

by centers with the necessary laboratory and surgical expertise in carefully selected patients (ASRM 2019, p. 1025).

94. ***Successful live births in adult females who underwent OTC during pre-menarche (childhood or early puberty) are extremely low—based on the reported cases in the literature, fewer than three individual patients in the whole world***. There have been two pre-menarche female children who had ovarian tissue cryopreserved and subsequently auto-transplanted as adults who were able to have spontaneous pregnancies and live births. The first was reported in 2015 of a pre-menarche child who underwent OTC at age 13 years in order to prepare for treatment of sickle cell anemia (Demeestere et al. 2015); the other was reported in 2018 of a 9 year old child who underwent OTC prior to treatment for B-thalassemia (Matthews et al. 2018). A third adolescent who had OTC performed at age 14 later had a live birth, and another ongoing pregnancy, but it was not reported if she had already had menstruation at the time of OTC (Rodriguez-Wallberg et al. 2021).

95. A systematic review found 16 studies with data specific to pediatric patients who had undergone fertility preservation for gonadotoxic cancer treatments (Corkum et al. 2019). The reviewers found that of 298 patients who underwent OTC under the age of 13 (which generally indicates pre-pubertal/pre-menarchal status), just 3 underwent surgery later on in adulthood to autotransplant their ovarian tissue (Corkum et al. 2019). The total number of females aged 0-20 who underwent ovarian tissue cryopreservation numbered 1019 individuals. Eighteen of these patients had ovarian tissue auto-transplanted back into the peritoneal cavity or within the remaining ovary. The median age of the patients who underwent OTC between 0-20 years who then subsequently had surgery to undergo autotransplantation was 19 years. The age at which the ovarian tissue was autotransplanted back into the patient was 24 years. The ovarian tissue grafts

were found to be functional up to 7 years after autotransplantation of graft placement. One patient who underwent OTC prior to menarche was able to achieve a live birth; the other live births were in females who had OTC performed after menarche but under 20 years of age. Thus, in all, of the 1019 patients who underwent OTC between 0-20 years of age, just 18 of the patients underwent surgery to autotransplant the ovarian tissue back into the peritoneal cavity; and of these 18, just 3 were pre-pubertal at the time of OTC. Among these patients who had OTC under age 13, and who then subsequently underwent autotransplantation of cryopreserved ovarian tissue in adulthood, ***just one achieved a live birth***.[7] The technique for OTC in this age group is not standardized and there is significant heterogeneity of both the cryopreservation and transplantation processes (Corkum et al. 2019). The authors caution: "The success of autotransplantation in women who were children at the time of OTC may take decades to be fully understood. In addition, while a few institutions did mention unsuccessful transplantations in girls 20 years of age and younger at the time of OTC, there is a risk of reporting bias toward publication of only cases in which fertility and hormone restoration was achieved" (Ibid, pg 2207). That is, the true denominator of how often OTC is performed in pre-pubertal female children may be unknown, and thus success rates of achieving a live birth over-estimated, because only successful outcomes get reported rather than all who attempt OTC as an attempt to preserve fertility. This kind of reporting bias confounds the reported success of this procedure. The review cautions that the efficacy of fertility restoration in patients who are prepubertal at the time of OTC cannot be determined at this time (Ibid).

96. The technology of oocyte in vitro maturation (IVM) has also been used as a fertility preservation technique in women. Recorded live births from IVM technology are extremely low,

[7] This is the patient reported in Matthews et al 2018 who was 9 years old at the time of OTC.

and there are significant challenges for utilizing the technique in pre-pubertal or early pubertal female children who have not yet undergone menarche.

97. IVM techniques have been used for decades and used in breeding programs for animal husbandry. The ability of the technology to be used in humans was not developed, as oocyte maturation with controlled ovarian stimulation protocols (COS) were being generated simultaneously. As such, with greater utilization and investment in medical and laboratory infrastructure to develop COS technologies, the successful live birth rates kept improving with this method; COS is now the overwhelming technological modality used to overcome barriers to achieving fertility for individuals who have completed pubertal transition, but cannot be used in pre-pubertal or early pubertal children/adolescents.

98. Because IVM can be theoretically accomplished without female pubertal maturation, there has been some investigation using ovarian tissue from pre or very early pubertal females for fertility preservation in children who have cancer, as this avoids the transfer of the preserved ovarian tissue back into the female when she grows into adulthood (Gilchrist & Smitz 2023). The reason for this approach is to avoid the risk of possible malignancy being reintroduced into the patient if ovarian tissue cryopreservation was performed for an oncological (cancer) diagnosis. Instead of re-transplanting the cryopreserved ovarian tissue back into the patient and allowing the physiologic maturation of the oocytes in the body (as described earlier in this report), the process of IVM takes the cryopreserved ovarian tissue and matures the oocytes outside of the female body ("ex-vivo"). The rationale for this is to completely eliminate the risk of potentially re-introducing malignancy when the OTC is used to preserve the fertility in females with a cancer diagnosis. With IVM, when the female is an adult and decides she would like to pursue pregnancy, the oocytes obtained from the OTC process are fertilized by a technique called intracytoplasmic

sperm injection (ICSI). If a blastocyst develops from this method, it is then transplanted into the patient's uterus.

99. The IVM technology has resulted in a wide range of maturation rates of cumulus oophorus complexes, with overall maturation rates of 39% +/- 23% (Segers et al 2020). Recall that the follicular cells surrounding the primary oocyte are essential to the maturation of the primary oocyte into the dominant follicle capable of being ovulated, and this process of follicular maturation only occurs at the pubertal transition in response to LH/FSH. In the IVM process, this step does not occur because the ovarian tissue cryopreserved during childhood is not re-transplanted back into the female patient from whence it came. Instead, the primary oocytes within the ovarian tissue are matured outside of the female body using a variety of protocols to accomplish this process, with varying degrees of success (as described above).

100. To date, the youngest child from whom mature oocytes have been obtained after IVM was aged 5 years (Segers et al 2015 pg 1228), with a maturation rate in 6 pre-pubertal girls of 18% (Segers et al. 2015 pg 1223, 1228) to 22% (Segers et al 2020, pg 2028). It is very important to realize that maturation rates do not guarantee a live birth will result from this process. As of 2021, there have been only 5 live births from embryos generated from fertilization of oocytes matured "in vitro"; 5 live births from over 500 patients in total who had in vitro maturation from oocytes retrieved from ovarian tissue; all were adults at the time of ovarian tissue retrieved and then matured "in vitro" (De Roo 2021, Tables 1 and 2). Crucially, compared to adult ovarian tissue, the ovarian tissue from premenarchal children appears to contain a relatively larger population of abnormal follicles, and follicle development and oocyte growth in culture has been shown to be compromised; because of this, it is hypothesized that the prepubertal ovary needs a "maturation phase" in childhood to gain optimal follicle function as an adult (Segers 2015 pg 1228).

Concerningly, it is possible that the oocytes harvested from ovarian tissue of pre-menarche children might lack the capacity to resume meiosis (Ibid). ***There have been no live births from the IVM from ovarian tissue obtained in premenarchal female children, and no live births from transgender men (natal females) who had been on testosterone prior to gender affirming bilateral oophorectomy*** (De Roo 2021 Table 1). Because of the low maturation rates and concomitant viable pregnancies, even in adults, the fertility potential of IVM is still under evaluation (Choi 2022, pg 6), as fertilization and embryological developmental capacities seem to be impaired (De Roo 2021, pg 6).[8]

101. ***In summary, the live birth rate for female adults who underwent OTC and IVM technologies as a means to preserve fertility during pre pubertal/early pubertal (premenarchal) development are extremely low: 3 live births for the use of OTC, and 0 for the use of IVM (Demeestere et al. 2015, Segers et al. 2015, 2020; Matthews et al. 2018; Rodriguez-Wallberg 2021). There are also 0 live births in adult transgender men (natal females) who have utilized these technologies whilst receiving testosterone for gender affirming care (De Roo 2021, Stolk 2023).***

102. Such data are in stark contrast to the cumulative live birth rate for controlled ovarian stimulation (COS) followed by in vitro fertilization (IVF). Recall that COS is performed in settings also where there are no contraindications to these procedures as no intrinsic pathological process occurs within the body, much like gender dysphoria. The key is that the technology can be utilized

[8] IVM is, however, one of the only ways to avoid reintroduction of malignancy in females who suffer from cancer and undergo fertility preservation, since it removes the requirement of auto-transplantation. For females who identify as transgender, it also offers a way to avoid ovarian tissue autologous transplantation, or endogenous gonadotropin stimulation and oocyte retrieval with subsequent oocyte cryopreservation, but again, this process is experimental (Stolk & Asseler 2023) and the use of IVM in female transgender men has not been successful in generating a live birth (Ibid pg 33).

only once puberty has advanced to the level of endogenous gamete maturation (Tanner 4 or 5). One study noted the live birth rate above 24 weeks gestation in over 14,000 patients can be up to 70% with >25 oocytes retrieved after controlled ovarian stimulation (Polyzos et al. 2018). Critically, these data also note the increased risks to females with this approach, such as ovarian hyperstimulation syndrome.

103. There are limitations in interpreting success of assisted reproductive technologies since protocols, patient selection criteria, and methods used rates vary widely between centers. It is important to keep in mind that the use of assisted reproductive technology in females carries risks compared to those who do not require these technologies to conceive (ACOG Committee Opinion No. 671, reaffirmed 2020).

B. Fertility Preservation Options for Males

104. In males, fertility preservation options are only experimental before the gametes are mature. Currently there is no way to "mature" an immature germ cell/spermatogonia. These immature germ cells/spermatogonia are cells in the male testes present at Tanner stage 2 of very early pubertal development. Recall from earlier in this report that males are born with immature gametes which have not yet entered the cellular division stage of meiosis. Physiologic puberty in males where the gametes undergo the process of maturation is called spermarche and occurs at Tanner stage 4. The process can only occur if LH and FSH are able to act at the level of the Leydig and Sertoli cells at puberty, to sustain the developing sperm cells from their immature diploid form to the haploid mature spermatozoa.

105. If this action of LH and FSH is "blocked" before the natural pulsatile release of GnRH in natal puberty ever occurs, followed in succession by exogenous estrogen administered in supraphysiologic doses (without a "break" in this process), it is unknown if spermatogenesis

could ever develop; there are no data of this ever occurring because there are no fertility outcome studies for male children who ever underwent this regimen at Tanner stage 2. There is a report of spermatocytes retrieved from an adult male matured in vitro, but these spermatocytes had already started the process of meiosis when they were further matured in vitro, resulting in one live birth (Tesarik et al. 1999). This is very different from a pre-pubertal or early pubertal male who does not have any spermatocytes, only germ cells.

106. Consequently, ***for pre- or early pubertal male patients, testicular cryopreservation in this age group as a way to preserve fertility remains investigational and is done only in clinical trials*** (Rowell et al. 2020; Nahata et al. 2020, Klipstein 2020). The technology relies on the ability to generate mature spermatozoa from pre-meiotic diploid spermatogonia, which is experimental. Current knowledge of this technique is limited to animal studies (Delessard et al. 2020, Ibtisham et al. 2017, Wang et al. 2020, Ibtisham et al. 2020). Progress within this field is slow, with an immense amount of work to be done regarding fertility preservation for boys and adolescents (Ntemou et al 2019, pg 2); there is no report of any of the proposed experimental approaches (both in vitro and in vivo) resulting in spermatozoa generation from human immature testicular tissue cryopreservation (Ibid, pg 8)

107. Testicular tissue cryopreservation in male children is conceptually very similar to ovarian tissue cryopreservation in female children. For example, in the case of pediatric cancer, a testicular biopsy is obtained and cryopreserved, and the immature cryopreserved spermatogonia can be placed back into the testes once treatment has completed. This process, however, has the risk of reintroducing malignant cells. It also has not been successful in generating mature spermatozoa or live births once adulthood is reached. There are ongoing trials investigating this process (Clinicaltrials.gov).

108. Testicular cryopreservation may not be possible in males who undergo GAC because of the changes to the testes caused by prolonged GnRHa, testosterone blockers, and estrogen administration (de Nie 2022).

109. There are some data that show the possibility of autotransplantation to an ectopically located site away from the testes, as well as methods to mature the immature spermatogonia "in vitro" by trying to "match" the internal conditions of puberty during the time when this would normally occur. All such methods are experimental (Wang et al. 2022; Ibtisham & Honoramooz 2020; Stolk & Asselar 2023).[9]

110. ***There have been no live births from testicular cryopreservation performed during pre- or early pubertal male development, since there is not currently the ability to mature spermatogonia from these specimens in humans.*** There has been a live birth after an oocyte was fertilized with mature sperm retrieved from an adult male who underwent in vitro spermatogenesis, but this occurred after meiosis had already started, up to the level of the pachystene stage of meiosis 1; the male had already completed puberty (Tesarik et al. 1999).

111. In sum, testicular cryopreservation as a method to preserve fertility in pre-pubertal or early pubertal children is still experimental. Maturation of immature spermatogonia/germ cells has not been demonstrated in humans.

[9] There is a method to mature spermatogonia in the testes of a different species called xenotransplantation. This technique injects the spermatogonia germ cells of one species into the testes of another species where they mature in the seminiferous tubules of that species (Wang et al., 2022). To date the only ability to generate mature spermatozoa from human immature spermatogonia in vitro has been shown in one ethically fraught study from China where male fetal germ cells were matured from the fetal testes of an aborted male fetus (Yuan et al. 2020, pg. 244-45).

C. Fertility Preservation is Unrealistic at Tanner Stage 2

112. Although risk of infertility is nearly certain for children who initiate GAC at Tanner stage 2 and there are no known ways to reliably preserve fertility at this stage, there are more data for fertility preservation *after* gametes mature in the later stages of puberty/adulthood.

113. Assisted reproductive options, including fertility preservation, *after* pubertal transition for both males and females, are well-documented, and consist of (1) spermatozoa cryopreservation for adult male patients, (2) use of conventional "IVF" technologies (generation of cumulus oophorus complexes using "in vivo" maturation of the oocyte in the female post-pubertal adult), and (3) OTC/IVM in adult female patients. The first two modalities are more accessible within the existing clinical infrastructure and have documented success rates for live births depending on the methods used (up to 70% one multicenter analysis) (Polyzos et al. 2018). As discussed, OTC/IVM are still relatively new; however live births have been achieved in adult females utilizing these technologies if they do not have any other options to help them achieve their reproductive goals.[10] Even so, it is crucial to acknowledge there are still risks to assisted reproductive technologies and centers have varying degrees of success. There are also higher

[10] The ASRM reports live births reported around the world after OTC was used for post-pubertal adults, with 130 live births for this method reported thus far. The live births for IVM, as discussed, have occurred in adult patients only, with a total of 5 live births reported thus far worldwide using this technique. As discussed extensively, these are very different populations compared to premenarchal female children. For patients without any other options to preserve fertility, such as those who have a childhood diagnosis of cancer and cannot wait for gonadotoxic treatment initiation due to undue risks this poses to their lives, OTC in female children and testicular tissue cryopreservation in male children are techniques which can and should be utilized ethically. However, for early pubertal children who do not have a physical locus of malignancy threatening their survival, it is not medically necessary to utilize these nascent technologies for which live birth outcomes are either non-existent or extremely rare. Once natal pubertal transition has occurred, these young people can make further fertility preservation decisions which have a much higher success rate and are more accessible later in adolescence or adulthood, if need be.

perinatal risks to females who undergo assisted reproductive technologies which need to be taken into consideration as well.

114. Encouraged to delay GAC until after puberty, young people also may decide they are more comfortable in their natal sex, do not want any medicalization, and still identify as transgender.

115. Data show that one of the primary reasons young people do not utilize fertility preserving measures is because they do not want to delay the hormonal GAC regimen (Harris 2019 pg 2454; Stolk & Asseler 2023 pg 30; Robinson 2023 pg 10). Increasing the age where one can receive hormonal GAC regimen would thus provide more time for young people to complete puberty and increase their access to well tested, more successful, and accessible fertility preservation technology should they need to do so.

116. In summary, fertility preservation technology at Tanner stage 2, when gametes are not mature, is nascent, inaccessible, and experimental. In contrast, assisted reproductive technologies for those who have completed puberty are more widely accessible with much higher success rates in achieving a live birth. The evidence base for medicalizing a child's gender identity at Tanner stage 2 is insufficient and low quality, with purported benefits not shown to outweigh the harms of the loss of functional physiologic bodily capacity (Abbruzzese 2022; Levine 2023; D'Angelo 2019; Block 2023; Biggs Sept. 2022). There is no indication, therefore, for gender identity to be medicalized through transitioning treatments when Tanner stage 2 of puberty is reached. Requiring young people to wait until adulthood to pursue transitioning treatments will allow young people who identify as transgender to realize their fertility goals without risks of iatrogenic infertility caused by gender affirming care administered too soon, and may mean they never need to access assisted reproductive technologies.

D. Fertility Preservation Counseling for Youth Receiving GAC is Inadequate

117. Unfortunately, despite the risks, studies have shown that discussions about fertility preservation with children and young adolescents with gender dysphoria are limited (Choi & Kim 2022). The hazards to reproductive function and fertility related outcomes of medicalized GAC limits the ability to effectively counsel patients, and there are no guidelines regarding fertility preservation for transgender individuals (Ibid.). Despite data showing that interest in future parenting is high among adult individuals who identify as transgender (Ainsworth et al. 2020), and that quality of life is noted to be significantly higher for transgender-identifying adults who have children (Choi & Kim 2022), data for pre or early pubertal children remain understudied, with up to one third indicating their feelings about parenthood may change in the future (Schwartz & Moravek 2021).

118. For adolescents who identify as transgender, data are quite mixed regarding fertility preservation counseling and fertility preservation techniques utilized. While one review of the literature found that up to 88-100% of adolescents in the included studies received fertility preservation counseling, the exact counseling rendered was not described, nor were validated tools identified for such counseling. Indeed, the authors note: "[T]he main limitation of this systematic review is the low quality body of evidence presented… [S]tudies … were cross sectional questionnaires, case series, or small sample size cohort studies with limited follow up time and lack of control groups; however, it is the best available data at this time" (Stolk and Asseler 2023 pg 35). Another study revealed a very low rate of just 13.5% of adolescents reporting they had received fertility preservation counseling (Stolk et al. 2023 Table 3), with another reporting up to 100% of fertility preservation counseling (Ibid). As for actual use of fertility preservation options, the rate ranged from 0% to 62%. This top value is an outlier and only applied to males who had

already reached spermarche; the majority of studies reported fertility utilization of <10%, with more males utilizing these technologies than females. And it is important to note that the mean age of these adolescents in all studies were all after the ages at which spermarche and menarche typically occur (Stolk and Asseler 2023 table 3). Most data consistently show that less than 5% of adolescents underwent fertility preservation procedures with gamete cryopreservation (Pang et al 2020, Choi & Kim 2022, Stolk and Asseler 2023). The ASRM, Endocrine Society, and WPATH all recommend fertility preservation counseling prior to initiation of GAC, but studies have raised concern that this standard is not being met despite growing evidence that gender affirming regimen has a detrimental impact on the potential for future fertility (Ibid.).

119. It is unknown how many pre- or early-pubertal children with gender dysphoria undergo counseling for fertility preservation prior to administration of GnRHa followed by cross sex hormones. There remain significant gaps and low utilization in the counseling and education surrounding fertility preservation for children and young adolescents at Tanner stage 2 of pubertal development in whom medicalized GAC has and is currently being offered for several years. In the United States, the first gender clinic was opened in 2007, yet we still do not have any data to help elucidate these phenomena aside from the limited reports I have just described.

120. In summary, inadequate fertility-preservation counseling calls into question the completeness of the informed consent process for the GAC regimen in Tanner stage 2 children and young adolescents. The only "fertility preservation" techniques for which long term data exist are those for individuals who have already matured through the pubertal transition and who have mature gametes. Thus, accurate representation of the evidence regarding fertility preservation in individuals who identify as transgender compels delay in endocrine interventions until after pubertal maturation of the gametes has occurred—that is, until much later in adolescence/early

adulthood. As mentioned earlier in the report, those seeking reversals of permanent sterilization even when they had undergone these procedures between the ages of 18-24 years of age is over 40% even in adults. And it is well established that even adults under age 30 have increased rates of sterilization regret compared to those older than age 30, even when they have had their own children. It is in the best interest of the child to reduce this risk of sterilization regret by delaying any hormonal manipulation of healthy physiologic function until at least 19 years of age. The delay in such hormonal manipulation will allow preservation of a child's open future in which adult reproductive goals are preserved.

VIII. Response to Plaintiffs' Experts

121. I have reviewed the opening expert reports of Dr. Armand Antommaria, Dr. Daniel Shumer, Dr. Meredithe McNamara, Dr. Aron Janssen, and Dr. Morissa Ladinsky.

122. Dr. Shumer claims on page 6 of his report that "sex is comprised of several components, including, among others…gender identity." He then states on page 7 that "everyone has a gender identity." But gender is a social concept; it has no locus on the physical body (Schwartz 2021, Biggs 2022) and therefore has nothing to do with the objective locus of sex. The physiologic function of sex is to reproduce the species; in mammals, this occurs by the internal fertilization of an ovum by a spermatozoan. The function of sex is binary.

123. Dr. Shumer also states that gender identity "is an internal and largely biological phenomenon" but it is also "understood" and "may evolve." It is unclear what he means by "largely biological phenomenon." Biological phenomena are tangible, immutable (Dorland's 29th ed). For example, it is a biological phenomenon that only female-sexed individuals can gestate. There is no objective measure of gender identity.

124. Dr. Shumer claims that attempts to "force" someone with gender identity to "align" with their "birth sex" is harmful. He does not describe what this means, but seems to assert that the actual physical, biological processes of healthy human physiological development, including sexual maturation and puberty, are somehow unhealthy and must be externally "forced." What *is* forced is trying to provide the facsimile of an opposite sex by administration of supraphysiologic doses of either testosterone in females, or estrogen in males, in an attempt to appropriate the appearance of the opposite sex. Only the medical establishment can force this kind of bodily modification; it is not physiologic.

125. On page 15 of his report, Dr. Shumer states that "GnRHa have no long-term implications on fertility." As demonstrated above, this statement is decidedly not true when GnRHa are begun at Tanner stage 2 of puberty and followed without pause by cross-sex hormones, as WPATH and the Endocrine Society recommend. Dr. Shumer may be referring to the use of GnRHa in children with central precocious puberty (CPP), but those patients undergo natural puberty at the natural time—unlike patients receiving puberty blockers as part of gender affirming care.

126. Dr. Shumer cites the PREFER study to support his claim that GnRHa have been "proven" to "not have long-term implications on fertility." The study actually showed there were insufficient data at the primary endpoint of the study to make firm conclusions regarding the proportion of women desiring a pregnancy but who did not achieve pregnancy 6 and 12 months after stopping all contraceptive methods (Martinerie et al. 2020, pg 536). In other words, these are women who desired pregnancy but did not yet achieve it—the key question the study was meant to address. It is reassuring that pregnancy *can* be achieved after GnRHa administration for CPP in females, but even the study authors state that the results need to be consolidated with a subsequent

study to assess fertility and infertility rates when women will have reached their mid-thirties (Ibid pg 536). In males, limited data exist on reproductive function after treatment for CPP with GnRHa; data on paternity rates and fertility are not available (Bangalore-Krishna 2019, pg 364). Therefore, Dr. Shumer's statement that "GnRHa have no long-term implications on fertility" is too strong even when confined to GnRHa used to treat central precocious puberty.

127. Dr. Shumer asserts that GnRHa are used at the onset of puberty (Tanner 2) until mid-adolescence and that "the decision to continue treatment will be continually evaluated." "Should pubertal suppression no longer be desired," he states, "GnRHA would be discontinued, and puberty would re-commence." This statement has not been proven because the only data we have are for children who were placed on this medication for CPP, not normally timed puberty. An international consortium continues to lament the lack of long-term outcome studies, especially to address concerns regarding impacts on bone mineral density and infertility when used in patients who identify as transgender (Bangalore Krishna 2019).

128. Dr. Shumer states on page 20: "Adolescents diagnosed with gender dysphoria who have entered puberty (Tanner Stage 2) may be prescribed puberty-delaying medications." This is misleading. Tanner Stage 2 occurs on average at age 10 in female children and 11 in male children, but the normal range is 2 standard deviations from those ages. Thus, in females Tanner stage 2 of puberty can occur at age 8 in normally timed puberty, and for males, at age 9. The normal distribution of ages in Tanner stage 2 of puberty are 8-13 for female children and 9-14 in male children. By use of the term "adolescence" the reader unaccustomed to what "Tanner stage 2" means may be led to believe that GnRHa are only given to adolescents, but that is not true. They are also given to children, which the AAP defines as up to 12 years of age (AAP Policy Statement, Age Limit of Pediatrics 2017).

129. Another key detail omitted by Dr. Shumer is that once GnHRa are given for a time, especially at Tanner stage 2 when gamete maturation has not yet occurred, GnRHa will prevent the maturation of primary oocytes and spermatogonia and may preclude gamete maturation (Bangalore Krishna et al. 2019, pg 365). If gametes cannot mature, administration of supraphysiologic doses of hormones to match those of the opposite sex has the risk of damaging immature gametes, and there is a high likelihood for permanent sterility, especially in males (Stolk & Asseler 2023; de Nie 2022). Dr. Shumer admits this fact later, on page 22 of his expert report: "While GnRHa themselves do not have long-term implications on fertility, ***it is necessary for a person to complete puberty to produce viable eggs or sperm.***" (Emphasis added). Yet he does not connect the dots. Since GnRHa drugs are used precisely ***to*** block natal pubertal transition, and viable gametes can only occur ***with*** pubertal transition, if pubertal transition is blocked by the GAC regimen, with puberty blockers at Tanner 2 followed by cross sex hormones, the gametes cannot mature, and therefore the risk of sterility is very high. Even WPATH SOC 8 acknowledges this concern and recommends fertility preservation before initiation of GnRHa therapy (WPATH 2022 section 12.10, 16.3). Dr. Shumer says it again on pages 24-25 of his report: "Progression through natal puberty is required for maturation of egg or sperm. If attempting fertility after previous treatment with GnRHa followed by hormone therapy is desired, an adult patient would withdraw from hormones and allow pubertal progression. Assistive reproductive technologies ***could*** be employed if needed." (Emphasis mine). He then cites a 2013 source that does not address early pubertal adolescents at all and refers to "transexual persons" who are adults—i.e., who by definition passed through puberty and whose gametes are already mature (T'Sjoen 2013). An adult patient who has not been administered puberty blockers followed by cross sex hormones beginning

at Tanner stage 2 of early puberty is not the same patient as a young person who has been subjected to this regimen.

130. I have discussed fertility preservation in detail earlier in this report. Fertility options in male children at Tanner 2 puberty blockade can be performed only if testicular cryopreservation is undertaken prior to starting the hormonal GAC regimen. The techniques for trying to mature spermatogonia from the testes of early pubertal male adolescents are still experimental and are not well studied in humans (except as proof of concept in animal studies), but there is no way to know if sperm matured this way (i.e., in vitro spermatogenesis) will be able to fertilize an ovum or if a live birth would result in humans. There has never been a live birth using sperm from a male who was administered GAC at Tanner stage 2, and there are no current data by which these young patients and their families can be assured their fertility and reproductive goals will ***ever*** be possible. The technology to mature spermatogonia in vitro and clinical infrastructure for this to occur in Tanner stage 2 males simply does not exist on a clinically relevant scale.

131. For female early pubertal children and young adolescents at Tanner stage 2, the "option" for fertility preservation is ovarian tissue cryopreservation as discussed earlier. There have been two patients who had live births after ovarian tissue was cryopreserved prior to menarche, and autotransplanted. A third patient had a live birth from ovarian tissue cryopreserved but the report did not describe whether or not menses had already started at the time of ovarian tissue cryopreservation. There are no data that a female young person who was administered GnRHa at Tanner stage 2 followed directly in succession by testosterone (the regimen of "gender affirming care") has ever had a live birth in adulthood. "There are no long term follow up studies studying the effect of puberty suppression and testosterone on gonadal function and gametes" (Stolk et al 2023, pg 3). The only reproductive outcomes data exist for post-pubertal females who

have taken testosterone alone, or GnRHa alone, each for a limited time period, *not* in direct succession. As discussed in this report, these are very different patient populations.

132. At Tanner stage 2, male gametes are immature spermatogonia. If gametes are "blocked" prior to the meiotic division of spermatogonia, not only will maturation halt, but also because GnRHa has blocked LH, the Leydig cells of the testes will not be capable of testosterone production. Since testosterone is inhibited, conversion to dihydrotestosterone (DHT) will not occur, preventing the physical maturation of the penis and scrotum. There are ***no*** data to show that males can regain this growth after pubertal blockade followed by exogenous supraphysiologic doses of estrogen. Estrogen in males will lead to hypospermatogenesis and eventually azoospermia, which will become irreversible after some time, as noted by the reference that Dr. Shumer used in his expert report. (T'Sjoen et al. 2013, pg 577). The peno-scrotal hypoplasia that develops from the GAC regimen initiated at Tanner stage 2 has significant ramifications if the male chooses, in adulthood, to undergo penectomy with penile inversion vaginoplasty. Peno-scrotal hypoplasia (an arrest in the growth of the male external genitalia from the time GnRHa were administered) is reported in the surgical literature to contribute to significant complications for these young patients and also increase the surgical risks, including bowel surgeries adding to the overall complications and surgical morbidity (Robinson et al 2023).

133. Dr. Shumer fails to discuss the key distinction between early pubertal children and young adolescents still at Tanner stage 2, on the one hand, and adults who have already gone through natal puberty, on the other. As mentioned earlier in this report, there are case reports of *adult* females who had been on testosterone for a period of time, stopped it, and then became pregnant (Light et al. 2014; Besse 2020). This is *not* the same patient population as an early pubertal child or young adolescent who received GnRHa before their gametes were even mature.

Ample data exist regarding fertility preservation options for adults as I have mentioned earlier in this report. Children who have puberty blocked and who are thus excluded from gamete maturation do not have these same fertility preserving options and warrant special consideration.

134. Dr. Shumer states that a young person exposed to GAC at Tanner 2 could, as an adult, "withdraw from hormones and allow pubertal progression." There are no data that this has ever occurred for a young person exposed to GAC beginning at Tanner stage 2. In fact, emerging data show that stopping gender affirming hormone treatment prior to orchiectomy did not affect possibilities for fertility preservation, since it is unknown if spermatogenesis can recover if gender affirming hormone treatment is stopped and how much time is needed for this purpose (de Nie 2021 pg 305). This may be why WPATH, ASRM, and the Endocrine Society recommend that fertility preservation options be discussed before transition (Coleman et al 2022, ASRM 2019, de Nie 2022, Ainsworth 2020). Dr. Shumer's lack of precision about the nature and timing of "hormones" obfuscates the fine details and differences in the risks of irreversible sterilization based on when natal puberty is blocked, which I have discussed at length.

135. Plaintiffs' expert Dr. McNamara further obscures the experimental nature of fertility preservation in pre-pubertal or very early pubertal males before any maturation of the spermatogonia. On pg. 15 of her report she states: "In a cohort of patients treated with puberty blockers starting at the onset of pubertal development (Tanner stages 2 and 3) and adding estrogen treatment starting at 16 years of age, histological examination of testicles showed normal appearing, immature sperm producing cells in the testes, ***suggesting*** those individuals had retained fertility potential" (emphasis added). Dr. McNamara's source for this statement shows that indeed, ***0%*** of males who had puberty blocked at Tanner stage 2-3, followed by estrogen at supraphysiologic doses, had any functioning mature spermatozoa in the testes at the time of

orchiectomy. All the spermatozoa were immature. Immature spermatogonia, which, as I explained at length in this report, and which is also reported in this very study (de Nie 2021 pg 299), *cannot* yet mature to spermatozoa "in vitro" or via germ cell transplantation (Klipstein et al. 2020 pg 5); functionally and practically, this renders the ability to actually preserve male children's fertility who undergo GAC at Tanner 2 impossible at this time, both pre- and post- GAC.

136. It is misleading for Dr. McNamara, or any physician counseling young male patients and their families about fertility preservation at Tanner stage 2, to declare that these data show it is "possible to preserve fertility." In doing so, she and other physicians obfuscate the reality of the limits of technological capacity of spermatogenesis (in vitro or via germ cell transplantation) and its purely experimental nature in humans. Discussion of "fertility preservation" when we do not have the actual capacity to deliver on any kind of male fertility preservation for those patients who undergo GAC at Tanner stage 2 of pubertal development is to discuss an experiment, one which at present is neither regulated nor closely or universally monitored. It is an experiment that has never been proven successful in humans and may never be. The only data that can be conveyed are the data that show banking of *mature* sperm. But mature sperm can be generated only if a male child is allowed to undergo endogenous puberty, which GAC prevents. This is why, in order to preserve an open future for a gender non-conforming young person to actualize their reproductive goals in the future, it is imperative to limit any gender affirming endocrine intervention until much later in adolescence, ideally over age 18, given the high rates of regret for sterilization procedures in young adults who have already had children. It is likely to be much higher for those who were sterilized as minors, before any fertility goals could ever be realized.

137. Children who have not even started puberty, or who are at the very earliest stages of puberty, do not have the emotional or intellectual capacity to be able to assent to a medicalized regimen that will cause them to lose functional bodily capacity to reproduce.

138. Hormonal interventions under the euphemism of gender affirming care are especially ethically compromised when one considers that the children to whom the regimen is recommended do not have any physical disease; the intervention itself *creates* the physiologic disease state for which the child will be dependent on the medical profession for the rest of their lives. This is the creation of iatrogenic disease in healthy children and adolescents which carries significant medical risks to numerous physiologic organ system functioning which are life-long.

139. Dr. Ladinsky states on page 23: "Providing transition-based medical care *can be* lifesaving treatment" (emphasis added). But if the patient has a diagnosis which requires *lifesaving treatment,* then why isn't this treatment recommended to all patients with such a diagnosis? There is no other clinical scenario where care considered to be "lifesaving" is ***not*** uniformly recommended to anyone who has a diagnosis which requires such intervention. To be sure, there are clinical scenarios where the diagnosis is uncertain or an intervention is experimental/emerging and shared decision-making is required. (Such interventions are given weak recommendations or are not typically recommended *because* the evidence quality is so low. An example in the field of gynecology is routine hysterectomy for the treatment of patients with the diagnosis of endometriosis). But it is completely at variance to have patients treated on an individualized basis for a diagnosis that requires "lifesaving" interventions; the recommendation should *always* be for that intervention if the diagnosis requires it, and a patient is free to agree to it or not. It is highly curious—and casts doubts on the enterprise—that in gender medicine, "lifesaving" care is only recommended *some* of the time; if it truly is "lifesaving," one would expect it to be recommended

all the time. Only if it *isn't* truly "lifesaving" could it follow that individual approaches to management are accepted. It cannot be both.[11]

140. My primary concerns as an obstetrician gynecologist are the unknown and known fertility effects that early pubertal suppression and cross-sex hormone administration has on female and male minors, both children and adolescents, during early pubertal development. Ample evidence exists for the inability of children to assent to these interventions on their healthy bodies where no physical locus of gender resides. (Abbruzzese & Levine 2023; Levine et al. 2022; Harris 2020). The process of physical alteration creates unethical risks that these children and young people are subjected to for the rest of their lives, which are life limiting. Moreover, our current ability to "preserve fertility" in children and young adolescents in whom puberty is blocked in Tanner stage 2 are nascent, largely unavailable, and experimental, making any discussion about "fertility preservation" for these children an exercise in disingenuousness.

141. It is my opinion that physicians who provide medicalized gender affirming care to minors believe they are helping children because they are following the guidelines set forth by leading professional medical societies in the United States. However, what is occurring now in the United States, in spite of much of the world (where these interventions were originally studied)

[11] As an example in obstetrics, a pregnant patient who experiences the diagnosis of eclamptic seizure requires immediate administration of medications such as magnesium sulfate to provide neuroprotection and reduce significant risk to her life; the intervention with medications to stop the seizure is *lifesaving*. Because it is a *lifesaving* intervention for all pregnant women who have the diagnosis of eclampsia, there is no shared decisionmaking to treat the woman with this diagnosis; the recommendation 100% of the time is to perform the intervention to stop the seizure. Another example is for pregnant women who have the diagnosis of complete placenta previa. It is 100% of the time recommended for all patients with this diagnosis to undergo cesarean to deliver their infant, and it is 100% *not* recommended (contraindicated) to undergo a vaginal birth for delivery. This is because the intervention of cesarean birth is *lifesaving*: it significantly reduces the risk of catastrophic maternal hemorrhage that a vaginal birth would uniformly cause for all women with the diagnosis of complete placenta previa.

curtailing endocrine interventions for minors based on systematic evidence reviews failing to show benefit over harms, can only be described as abnormal treatment behavior (Singh 1981). In my opinion, this is due in large part to established medical authorities in the United States, both organizationally and within the prevailing medical literature, reversing the tenets of beneficence and non-malfeasance to suit the profession and not necessarily the patient; such misrepresentation of the evidence can be considered coercive. The reversal of the ethical tenets of beneficence and non-malfeasance by major medical organizations has manipulated their members and created an unconscious fear in clinicians that gender dysphoria, or any manifestation of gender incongruence, carries such a poor prognosis it cannot be treated in any way other than the "gender affirming care" regimen, despite the poor evidence for doing so.

IX. Conclusion

142. For these reasons, I conclude that the Alabama Vulnerable Child Compassion and Protection Act is based on medical facts and serves to protect minors from unethical experimentation. The medical profession has not only failed to regulate itself, but is actively promoting such experimentation despite the known harms to vulnerable minors.

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Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril 2019;112:1022-33. https://doi.org/10.1016/j.fertnstert.2019.09.013

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Ibtisham F, Wu J, Xiao M, et al. Progress and future prospect of in vitro spermatogenesis. Oncotarget, 2017, Vol. 8 (no. 39), pp:66709-66727

Wang D, Hildorf S, Ntemou E, et al. Characterization and Survival of Human Infant Testicular Cells After Direct Xenotransplantation (2022) Front. Endocrinol. 13:853482. Doi: 10.3389/fendo.2022.853482

Yuan Y, Li L, Cheng Q, et al. In vitro testicular organogenesis from human fetal gonads produces fertilization-competent spermatids. Cell Research 2020; 30:244-255
Levine S, Abbruzzese E, Mason J. What are we Doing to These Children? Response to Drescher, Clayton, and Balon Commentaries on Levine et al., 2022. Journal of Sex and Marital Therapy 2023, Vol 49, No. 1, 115-125 (78)

Schwartz A, Moravek M. Reproductive potential and fertility preservation in transgender and nonbinary individuals. Curr Opin Obstet Gynecol 2021, 33:327-334 (54)

T'Sjoen G, Van Caenegam E, Wierckx K. Transgenderism and reproduction Curr Opin Endocrinol Diabetes Obes 2013, 20:575-579

Robinson I, Carswell J, Boskey E, et al. Gender Surgery in Adolescents and Young Adults: A Review of Ethical and Surgical Considerations. Plast Reconstr Surg. 2023. DOI: 10.1097/PRS.0000000000010325

Negenborn VL, van der Sluis WB, Meijerink WJHJ, Bouman MB. Lethal Necrotizing Cellulitis Caused by ESBL-Producing E. Coli after Laparoscopic Intestinal Vaginoplasty. J Pediatr Adolesc Gynecol. 2017 Feb;30(1):e19-e21 doi:10.1016/j.jpag.2016.09.005

Kalin NH: Reassessing mental health treatment utilization reduction in transender individuals after gender-affirming surgeries: a comment by the editor on the process(letter). Am J Psychiatry 2020;177:765

Singh B, Nunn K, Martin J, Yates J. Abnormal treatment behaviour. British Journal of Medical Psychology (1981) 54:67-73

Angela C.E. Thompson, MD, MPH, FACOG
Curriculum Vitae

651-410-4140

Present Academic Rank and Position

Attending Physician - OB Hospitalist Group, 02/2021 – present

Consultant Physician (supplemental coverage)– Mayo Clinic Department of Obstetrics and Gynecology Rochester, MN USA 11/2021 – present

Previous Professional Positions and Major Appointments

Consultant - Division of Obstetrics, Department of Obstetrics & Gynecology, Mayo Clinic, Rochester, Minnesota
04/2017 – 01/2021

Instructor in Obstetrics and Gynecology - Mayo Clinic Alix School of Medicine and Science
06/2014 – 01/2021

Senior Associate Consultant - Department of Obstetrics & Gynecology, Mayo Clinic, Rochester, Minnesota
05/2014 – 01/2021

Attending physician, Obstetrics and Gynecology - United Family Hospitals and Clinics, Shanghai, China
2012 - 2014

Attending physician, Obstetrics and Gynecology - Franciscan Skemp Medical Center, Inc., Mayo Clinic Health System - Franciscan Healthcare in La Crosse, Mayo Clinic Health System, La Crosse, Wisconsin
10/2010 - 12/2013

Attending physician, Obstetrics and Gynecology – 02/2010-10/2010 UW Health Watertown, WI; BDCH Beaver Dam, WI

Attending physician, Obstetrics and Gynecology - Altru Health System/Grand Forks Clinic, North Dakota
02/2008 - 01/2010

Certification

Board Certifications
American Board of Obstetrics and Gynecology
Obstetrics and Gynecology 2012 - Present
American College of Obstetricians and Gynecologists
Fellow, Obstetrics and Gynecology 2012 - Present

Licensure

North Dakota (Medicine and Surgery) 01/2008 - Present
Wisconsin (Medicine and Surgery) 01/2010 - Present
Minnesota (Medicine and Surgery) 11/2013 – Present
Texas (Medicine and Surgery) 02/2021 - Present
Florida (Medicine and Surgery) 12/2020 – Present
Arkansas (Medicine and Surgery) 02/2021 – present
People's Republic of China 03/2012 – 04/2014

Committees

Minnesota Department of Corrections Task Force on Justice Involved Women and Girls
Appointed 8/2022, reappointed 1/2023
Minnesota Mortality Review Committee. Appointed 2019 - 2021

Education

University of Minnesota Medical School, Minneapolis, Minnesota – Medical Fellow, Department of Obstetrics, Gynecology, and Women's Health 06/2004 - 06/2008

University of Utah School of Medicine, Salt Lake City, Utah - MD 09/2000-
05/2004

Yale University School of Medicine, New Haven,
Connecticut - MPH, Master of Public Health and Epidemiology 09/1998 - 05/2000

University of Wisconsin - Madison, Madison, Wisconsin - BS 09/1992 - 05/1996

Honors and Awards

CREOG National Teaching Award –American College of Obstetrics and Gynecology, Council for Resident Education in Obstetrics and Gynecology. Awarded to faculty by the residents in Obstetrics and Gynecology at Mayo Clinic - 06/2019

Teacher of the Year Award – Mayo Clinic Alix School of Medicine - 06/2019

Raymond J. Albrecht Award - University of Minnesota Department of
Obstetrics, Gynecology, and Women's Health
Awarded to the graduating resident exemplifying the highest values of the practice
06/2008

Arnold P. Gold Foundation Humanism and Excellence in Teaching Award
- Arnold P. Gold Foundation – 2006

Best PGY-2 Teaching Resident - University of Minnesota Medical
School, Minneapolis, Minnesota - 2006

Additional Education

Royal College of Obstetricians and Gynecologists
World Congress Annual Meeting
London, United Kingdom

06/2019

ACOG District II Annual Meeting
ACOG District II, New York, New York
10/2014, 10/2015, 10/2016, 10/2018, 10/2019

American College of Obstetrics and Gynecology (ACOG)
Department of Patient Safety and Quality Improvement, Washington DC, United States of America
04/2017 - 04/2017

National Rural Health Association Conference
Obstetric Care and Hospital Closures in Rural Areas, San Diego, California
05/2017 - 05/2017

High Risk and Critical Care Obstetrics
Symposia Medicus
05/2016

Society of Obstetrics and Gynecology Canada
ALARM course, Winnipeg, Manitoba
10/2016 - 10/2016

Management of the Labour Ward
Royal College of Obstetricians and Gynecologists, London, United Kingdom
06/2015 - 06/2015

Administrative Responsibilities, Committee Memberships

Mayo Clinic Rochester, MN USA
OB/GYN Quality Committee
Active Member 2016 - 2021
Department of Obstetrics & Gynecology
FBC Inpatient Practice Group
Active Member 2014 - 2021
FBC Labor & Delivery / Triage Practice Group
Active Member 2014 - 2021
Perinatal Practice Group
Active Member 2014 – 2021

Academic Career Development
Mayo Clinic Quality Fellow, Silver Certification 2021

American Congress of Obstetricians and Gynecologists (ACOG) Quality and Safety for leaders in Women's Health Care
Washington, District of Columbia
04/2017
Professionalism 1
Office of Leadership and Organizational Development
Rochester, Minnesota
05/2014
Healthy Dialogue
Office of Leadership and Organizational Development

Rochester, Minnesota
05/2014
Leading with Emotional Intelligence
Office of Leadership and Organizational Development
Rochester, Minnesota
08/2015

Professionalism 2
Office of Leadership and Organizational Development
Rochester, Minnesota
08/2015
Communication in Healthcare
Office of Leadership and Organizational Development
Rochester, Minnesota
08/2015

Professionalism 3
Office of Leadership and Organizational Development
Rochester, Minnesota
06/2016

Professional Memberships and Societies

Professional Memberships and Services

American College of Obstetricians and Gynecologists (ACOG)
Member 2012 - Present

Royal College of Obstetricians and Gynaecologists
(RCOG) Associate Member 2019- Present

Education Interests and Accomplishments

Teaching

OB Clinical Skills workshop
Instructor
Mayo Medical School
Rochester, Minnesota
07/2014, 07/2015, 07/2017, 07/2020

Mayo Clinic Department of Obstetrics and Gynecology
Clinical Reviews
OB emergency Simulation: Maternal Code
Rochester, MN
11/2016, 11/2017

MMSI Surgical Skills lab instructor
Mayo Medical School
Rochester, Minnesota
03/2015

Intrapartum Fetal Monitoring Review
Mayo Clinic Department of Ob/Gyn

Rochester, Minnesota
01/2015

Chief Case Review
Mayo Clinic OB/Gyn Residency Program
Rochester, Minnesota
12/2014

Presentations Extramural

National or International
Invited
National Rural Health Association Conference
Obstetric Care and Hospital Closures in Rural Areas
San Diego, California
05/10/2017
Oral
Differences Between Hospitals in Cesarean Rates for Term Primigravadis With Cephalic Presentation
Society for Gynecologic Investigation 2005 Annual Meeting
Houston, Texas
Poster
Acute Drug Abuse, Epidemiology and Local Trends
American Public Health Association Annual Meeting
Chicago, Illinois
1999
Regional
Oral
Macrophage Chemoattraction Protein-1Levels in Ovarian Cancer 'Matched' Tumor Specimens: Coorelation Between Macrophage Infiltration and Angiogenesis
University of Minnesota Resident Research Day
Minneapolis, Minnesota
05/2008

Clinical Practice, Interests, and Accomplishments

Maternal and child health quality; safety practices in both developed and low-resource settings. Volunteer activities: Medical service to Seguin and Jacmel, Haiti.

Research Interests and Accomplishments

7/2006-5/2008: University of Minnesota Dept of Gynecologic Oncology Research assistant; Investigated the role of MCP-1 production at the time of a secondary cytoreductive procedure amongst patients with ovarian cancer and how it correlates with increased markers for angiogenesis and with poor clinical outcome.
6/2003-5/2004: University of Utah Department of Obstetrics/Gynecology / Utah State Dept. of Health, Clinical research assistant; Contributed to clinical research in cesarean delivery rates and differences between hospitals in Salt Lake City.
5/2001-7/2001: University of Utah School of Medicine, Dept of Physiology, Experimental research assistant; Helped conduct research studying surfactant production in neonatal respiratory distress syndrome.
1/2000-5/2000: Yale University Dept of Molecular, Cellular, and Developmental Biology; Teaching Assistant to undergraduate Developmental Biology course.
5/1999-8/1999: United States Public Health Service, Eastern Arizona Office of Environmental Health and Engineering; Assisted in the development and implementation of injury prevention programs within four Native American Nations in the southwestern United States.

12/1996-4/1997: National Institute of Hygiene and Epidemiology, Hanoi, Vietnam: Research assistant
Contributed to ongoing research investigating enteric disease in children under five years of age.

Peer-reviewed Articles

1. Kim S., King A., Parikh P., Sangtani A., Shazly S., Brodrick E., **Thompson A**. Optimizing Post-Cesarean Opioid Prescription Practices at Mayo Clinic: A Quality Improvement Initiative. Am J Perinatology 2022; 39(04): 337-341; doi:10.1055/s-0041-1739491

2. Shazly S, Ahmed I, Radwan A, Abd-Elkariem A, Ell-Dien N, Ragab E, Abouzeid M, Shams A, Ali A, Hemdan H, Hemdan M, Nassr A, AbdelHafez A, Eltaweel N, Ghoniem K, Saman A, Ali M, **Thompson A.** Middle East Obstetrics and Gynecology Graduate Education (MOGGE) Foundation Practice Group. MOGGE Foundation Practice Guidelines: Prelabor rupture of membranes; Practice Guideline No. 01-0-19. *Journal of Global Health*. (2020); doi:10.7189/jogh.10.010325

3. Warner LL, Hunter Guevara LR, Barrett BJ, Arendt KW, Peterson AA, Sviggum HP, Duncan CM, **Thompson AC**, Hanson AC, Schulte PJ, Martin DP, Sharpe EE. Creating a model to predict time intervals from induction of labor to induction of anesthesia and delivery to coordinate workload. *International Journal of Obstetric Anesthesia* (2020); doi: https://doi.org/10.1016/j.ijoa.2020.12.004

4. **Fischer A**, LaCoursier Y. Differences Between Hospitals in Cesarean Rates for Term Primigravidas With Cephalic Presentation. *Obstetrics and Gynecology.* 2005; 105:816-21. ***(****former last name of 'Fischer')*